Original Article

Spectrum of Inherited Metabolic Diseases in neonates and children presenting at Izzat Ali Shah Hospital, Wah Cantt.

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[1,2,5,6] *Conception of study*
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Abstract

Objective: To determine the frequency of various Inherited Metabolic Diseases (IMDs) in clinically suspected neonates and children in relation to age, gender, and distribution in rural and urban areas.

Materials and Methods: A total of 275 symptomatic neonates and children were enrolled for IMDs. A complete medical history, baseline biochemical tests, cerebrospinal fluid analysis, arterial blood gases, anion gap, serum ammonia, lactate, and urinary ketones were assessed. Any significant microbiological cause for the presenting symptom was excluded. For screening of Inborn Metabolic Error simple Heel prick test was done on PerkinElmer 226 filter paper in newborns and infants. Samples were sent to Jordan for analysis. High-performance liquid chromatography combined with tandem mass spectrometry (LC-MS/MS) was the technique used in the screening of a variety of IMDs. The frequency of Inherited Metabolic Diseases and their relation with age, gender, and location was determined using the chi-square goodness of fit test. A p-value ≤ of 0.05 was considered statistically significant.

Results: Of the 275 subjects screened, 47(17%) had an inherited metabolic disorder, of which 27 were male and 20 were female with a Male to Female ratio of 1.35:1. The difference in metabolic disorders was significantly different between age (p=0.01) and gender (p=0.04). Of the diagnosed cases G6PD disorder was found to be the most frequent disorder 14 (29.79%) of the total diagnosed cases, followed by Aminoaciduria in 9 (19.15%) and Carnitine Uptake Defect in 7 (14.8).

Conclusion: The cases detected to have IMDs revealed a significant prevalence. G6PD was detected as the most frequent disorder. A simple Heel prick test on PerkinElmer 226 filter paper is a useful method to detect IMDs, though confirmation is usually required by other tests.

Keywords: Inherited Metabolic Disorders, hemoglobinopathies, Aminoaciduria.

Introduction

Inherited Metabolic Diseases (IMDs) are a variety of clinical conditions occurring due to the lack of a single enzyme or transporter in a metabolic pathway. This leads to the accumulation of toxic intermediate metabolites in the body of a neonate.[1] The buildup of such metabolites leads to clinical symptoms such as vomiting, lethargy, hypotonia, tachypnea, convulsions, developmental delay, or mental retardation. Most of these disorders usually manifest during the first week of birth when the infant starts feeding. Nevertheless if undiagnosed at this stage they present later along with other severe conditions such as sepsis, encephalopathy, pulmonary hemorrhage, metabolic acidosis, and seizure. The treatment at this stage becomes very difficult and challenging.[2]

So far over 1000 inherited metabolic diseases/inborn errors of metabolism (IEMs) have been stated and among them, 200 of such illnesses can be treated if diagnosed early.[3] Over the past decades the genetic defects of numerous inherited metabolic diseases have been recognized. Novel treatment options are now in hand and have enhanced the life expectancy for several patients with inherited metabolic diseases.[4] Global statistics have shown that IEMs related mortality rate is 33% or more in low and middle-income countries, causing at least 23529 annual casualties which internationally contribute a share of 0.4% to the global child mortality.[5]

Most of these disorders are diagnosed through screening programs in newborns recognized in many developed countries. Pakistan is a developing country with a population of more than 220 million and unfortunately does not have any screening program devised for newborns at the local or national level to date. There are few studies conducted in Pakistan on the local population on the subject because a very small number of centers are currently offering diagnostic facilities for specific metabolites.[3] Disorders of IEM must be detected and treated as early as possible. Lack of diagnostic facilities is a contributing factor in the delay in the treatment of these illnesses. Neonatal screening plays an important role in early diagnosis, and the use of tandem mass spectrometry has increased the number of diseases that can be detected.[6]

Tandem mass spectrometry is a standard technique used for screening more than 50 metabolic disorders in newborns which have made the diagnosis of IEMs more efficient. It has improved specificity and sensitivity for dried blood spot analysis. High-performance liquid chromatography combined with tandem mass spectrometry (LC-MS/MS) is an analytical instrument with a high turnover of tests. It can detect amino acid and fatty acid disorders within a very short time. Detection of these two metabolic components helps in the screening of more than 50 metabolic disorders.[7] As a most recent advancement, genetic technology is more helpful for newborn screening of IMDs in newborns.[8] Genetic mutations are the focal error in all metabolic diseases Therefore, precise genetic analysis is mandatory for the patient before proceeding for treatment.[9]

This study aimed to screen suspected cases of IEMs in clinically suspected neonates and children in NICU and pediatrics OPD of Izzat Ali Shah Hospital Wah Cantt along with their relation to age, gender, and distribution in rural and urban areas.

Materials and Methods

Study design and study population:

This descriptive cross-sectional study was carried out conducted at the NICU and Paediatrics OPD of Izzat Ali Shah Hospital, Wah Cantt. from Sept 2017 to March 2020. The study was approved by the ethics committee of the hospital and the informed written consent was taken from the parents of all participants.

A total of 275 neonates and children were enrolled with ages ranging from 1 day to 11 years. Patients with symptoms like reluctance to feed, vomiting, hypoglycemia, metabolic acidosis, hypotonia, and refractory seizures were included in the study. They also had a history of previous unexplained death in the siblings. Investigations conducted at the hospital laboratory included complete blood picture, blood cultures, C-reactive protein, liver, and kidney function tests, serum electrolytes, PT/APTT, cerebrospinal fluid analysis, arterial blood gases, anion gap, serum ammonia, and lactate and urinary ketones. Any significant microbiological cause for the presenting symptom was excluded. Neuro-imaging was done in some cases to exclude any cause for symptoms relating to CNS disorders. In order to exclude IEM simple Heel prick test was done on PerkinElmer 226 filter paper in newborns and infants. This paper was provided by Zahra Beau (ZB) Foundation. As the screening of Inherited Metabolic Diseases (IMDs) is expensive in Pakistan so this diagnostic facility was provided by the ZB foundation on a charity basis. All the samples were sent to Med Labs, Jordan for analysis by ZB

Foundation. High performance liquid chromatography combined with tandem mass spectrometry (LC-MS/MS) was the technique used in the screening of these cases. Sampling was done for screening of primary disorders such as Galactosemia, Cystic fibrosis, congenital hypothyroidism, congenital adrenal hyperplasia, phenylketonuria, glucose 6phosphate dehydrogenase (G6PD), sickle cell anemia, and other hemoglobinopathies. Also, screening for fatty acid oxidation disorders (e.g. Carnitine uptake defect), organic acid disorders (e.g. Malonic acidemia, Propionic aciduria), amino acid disorders (e.g. Maple syrup urine disease, homocystinuria), and lysosomal storage diseases were done.

Data was collected and analyzed using SPSS version 19. A p-value < 0.05 was considered significant. The frequency of Inherited Metabolic Diseases in 47 subjects was calculated and its relation with age, gender, and the location was determined.

Results

Out of 275, 47 (17%) patients were tested positive for either one or two metabolic diseases. The difference in metabolic disorders was statistically significant between males and females: X^2=4.235, p=0.04, more common in males 27 (57.4%) than females 20 (42.5%). 17-OH Progesterone deficiency, Cystic Fibrosis, and Carnitine uptake defects were more common in males. Whereas Galactosemia, organic acid disorders, 17-OH Progesterone deficiency & Malonic Acidemia were more common in females (Figure 1).

The age of these patients ranged from 2 days to 6.5 years. Cystic fibrosis with Carnitine uptake defect and with G6PD deficiency was more common in patients with age less than 60 days and Aminoaciduria was more common in patients with age more than 60 days. The difference in the distribution of metabolic disorders in different age groups was statistically significant: X^2=6.618, p=0.01(Table 1), with higher frequency in age >60 days (Figure 2). The difference is also significant in terms of gender (p=0.04).

Our study included 26 patients from the rural and 21 patients from the urban area. G6PD deficiency was common in both patients coming from rural or urban areas. Patients belonging to urban areas had more incidence of combined defect of cystic fibrosis and G6PD deficiency. Whereas patients from rural areas presented with a sole disorder of 17-OH Progesterone deficiency and organic acid disorders. They had combined metabolic errors in Cystic Fibrosis and Carnitine uptake, 17-OH progesterone, and Malonic academia (Figure 3). The place of residence had no relation with the IMDs in children; X^2=0.265, p=0.607.

Table 1: Chi-square test goodness of fit test showing association of IEM with Age. Gender & Location of patients

Variable	*Chi-square value*	*P-value*
Gender	4.235	0.04
Age	6.618	0.01
Location	0.265	0.607

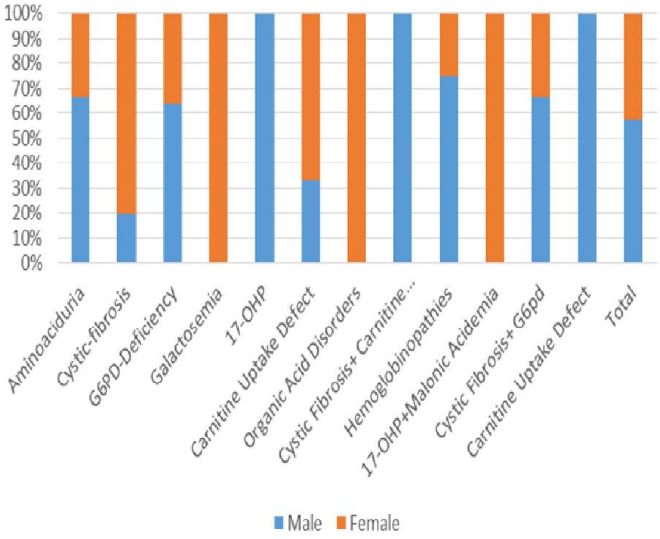

Figure 1: The statistical analysis of IMDs between male and female cases (n=47)

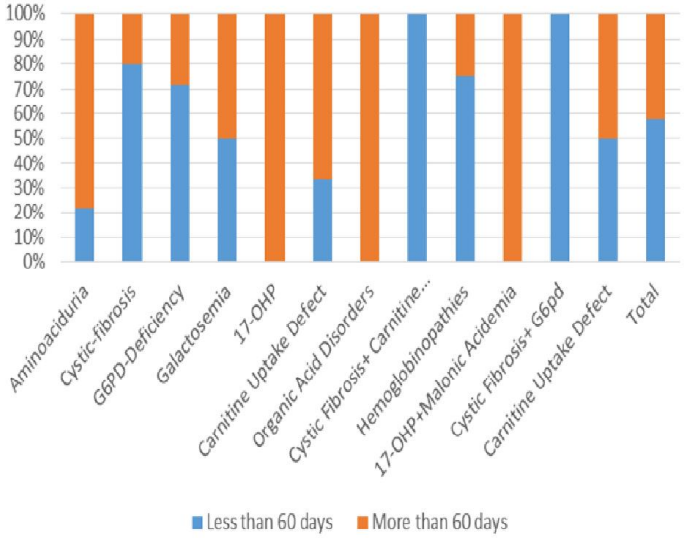

Figure 2: The statistical analysis of IMDs in relation to the age of patients (n=47)

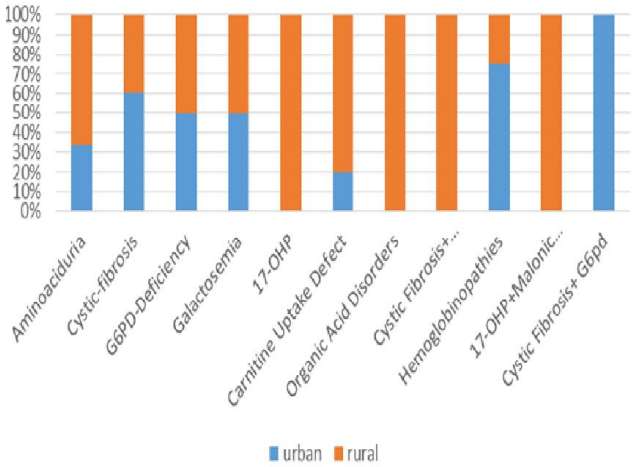

Figure 3: The statistical analysis of IMDs between rural and urban cases (n=47)

Discussion

Inherited metabolic diseases (IMDs) or Inborn errors of metabolism (IEMs) are characteristic clinical disorders that arise due to a single faulty gene that fails to metabolically regulate a particular biochemical pathway.[10] In IMD mutations occur in DNA coding for a precise protein, either enzyme, receptor, transport medium, membrane pump, or structural component. [11] Although IEMs are discretely rare but they collectively have high incidence and may lead to considerable mortality or long-term morbidity. [12] Often, there is a pre-existing history of an affected child in the family of such patients. Current research data regarding IMDs in Pakistan has shown a significant prevalence and Non-ketotic hyperglycinemia is the topmost disorder.[12] The timely diagnosis of IEM and early initiation of specific treatment may be life-saving in these patients.

The purpose of the current study was to screen and diagnose the distribution of different IEMs in infants coming to the tertiary care hospital both from rural and urban areas. We found a significant number of positive cases while conducting the test. In this screening study, 17% of clinically suspected cases were diagnosed to have metabolic disorders which are in accordance with the published data.[14] G6PD disorder was found to be the Most disorder in 29.79% of diagnosed cases followed by Aminoaciduria 19.15% and Carnitine Uptake Defect 10.64%. Similar results were found by Gul et al except for Amino acid metabolism which they found as the most common defect in 33.33% of cases.[15] Lodh and Kerketta quoted the incidence of G6PD deficiency and cystic fibrosis as 24.18% and 6.59% respectively which are to some extent in agreement with our findings.[14] Recently, a study carried out by Kaifi et al has highlighted the G6PD deficiency, Aminoaciduria, and Carnitine Uptake Defect as top-ranked IEMs though with different percentages.[16] In another study Sharma et al also documented G6PD deficiency as the most prevalent disorder but contrary to our findings they reported a very high incidence of 44% of the total diagnosed cases.[17] Cantu´-Reyna et al found G6PD deficiency and hemoglobinopathies as the most frequent disorders.[18]

Echeverri et al screened different IDM and listed aminoacidopathies as the commonest disorders followed by organic aciduria and Lysosomal storage disorders.[19] In our study the most frequent disorder was G6PD deficiency which is in accordance with the global incidence. The variation of detection of different IMDs is of course due to ethnic and regional origin. In Spain, the only IMD detected in all communities is PKU. In the present picture, there is a severe need for a more screening program to find the epidemiological statistics about the disease burden. In our country, due to more number of consanguineous marriages and big family size, we assume that these metabolic diseases along with rare disorders are prevalent. Forty-seven (47) cases of 13 different disorders were diagnosed in our study. The diagnosis of inherited metabolic disorders is currently rising in Pakistan. Many factors including economical, educational, and unawareness regarding disease complications are the major barriers in diagnosis.

Conclusion

The spectrum of inborn metabolic disorders is wide in our population and the cases detected to have IMEs revealed a significant prevalence. G6PD was detected as the most frequent disorder followed by Aminoaciduria and Carnitine Uptake Defect. There is more need to counsel the people about IMDs as well as developments in early screening for such disorders to protect them from future complications. A simple Heel prick test on PerkinElmer 226 filter paper is a useful method to detect IMDs, though confirmation is usually required by enzyme analysis or genetic testing.

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