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ORIGINAL ARTICLE

Clinico-Biochemical Presentation of Classical Organic Aciduria Presenting as Intoxication in Tertiary Care Hospital of Peshawar

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ABSTRACT

Background: About 5 million children died in 2017 in developing countries alone, amongst them 15-20% are due to inherited metabolic disorders. Inherited metabolic disorders like Methyl Malonic Aciduria, Isovaleric aciduria, Glutaric Aciduria type 1, Urea cycle defects, Maple syrup urine disease & multiple carboxylase deficiency present mostly as intoxication, ataxia and convulsions

Objective:To find the pattern of classical organic aciduria in children of different age and gender

Methodology: This cross-sectional descriptive study was conducted at Paediatrics department of Town Women & Children Hospital, Peshawar from Aug 2018- Aug 2020. Patients aged 0-24 months were included in the study based on inclusion criteria.Clinical data, preliminary investigations and urinary organic acids profile were collected. Data were analysed using SPSS version 21.

Results: Out of 178 total patients, 36 patients were diagnosed with classical Organic aciduria in this present study. Mean age of the study population was 0.865+/- 1.07654 years and range of 1 - 2 years. About 20(53%) cases were males, while 16(47%) cases were females. Major clinical and biochemical findings included seizures, feeding difficulties, developmental delay, neurological impairment, and motor weakness, hypoglycemic and metabolic acidosis.

Conclusion: The cases positive for inherited metabolic disorder showed a significant prevalence. Methyl Malonic Aciduria was the commonest of the OAs found in Northern areas of Pakistan followed by 3- Methyl Glutaconic aciduria.Simple heel prick test alongside blood gas analysis and confirmatory test by urinary Gas Chromatography Mass Spectrometry were helpful in diagnosis of such inherited metabolic disorder.

Keywords: Intoxication; Organic aciduria;Ethyl Malonic aciduria; Fumaric Aciduria

INTRODUCTION

About 5 million children died in 2017 in developing countries alone, amongst them 15-20% are due to inherited metabolic disorders (IMDs). [1] Classical Organic Aciduria (OA) are a group of IMDs due to deficiency in enzymes involved in intermediate metabolic pathways of amino acid, carbohydrate and fatty acid degradation resulting in accumulation of toxic metabolites usually organic acids in brain and other tissues. Mode of inheritance is autosomal recessive. Consanguinity increases risk of IMD's.[2]

Prevalence is variable between regions, in South East Asia; it is 1 in 800 to 1 in 2500. Incidence is ten times more Pakistani origin patients (1:318) as compared to white patients (1:3180) in a study at West Midland United Kingdom.[3]IMDs have a variable spectrum of incidences individually from 1 in 10,000 to 1 per 1000,000 live births.[4] Together their frequency is found around 1 in 3000 live births. More than 65 different types of OAs are described.[5]Organic aciduria is relatively rare in UK, USA and other western countries. Individually IMDs are rare but collectively their incidence is around 1 in 800.[6]In a famous British study of Inherited Metabolic disorders done in West Midland during 1999-2003 it was reported that the incidence of OA increased to 12.6 /100,000 from 3.7/100,000 owing to fact that 10% of population was ethnic and Black minority group.[7] OA are relatively more prevalent in South east of Asia.[8] Many studies have reported a higher prevalence of OA in India, Iran, Bangladesh, Pakistan, Afghanistan and China.[9,10] OA includes Methyl malonic aciduria, Ethyl Malonic aciduria, Propionic aciduria, Isovaleric aciduria, Maple Syrup Urine disease, Glutaric aciduria etc.[11]

There are very few reported studies regarding incidence of metabolic disorders in Northern areas due lack of resources for comprehensive testing of such disorders and lack of newborn screening. IMDs like Methyl Malonic Aciduria, Isovaleric aciduria, Glutaric Aciduria type 1, Urea cycle defects, Maple syrup urine disease & multiple carboxylase deficiency present mostly as intoxication, ataxia and convulsions.[12] Most of them have an initial symptoms free period after birth but after gradual accumulation of metabolites intoxication symptoms such as increasing drowsiness, poor feeding, wasting and neurological symptoms like fits are seen. Patients can present clinically in decompensation with developmental delay, seizures, hypotonia and failure to thrive. They can have an acute and intermittent late onset form or chronic progressive form.[13]

It is vital to look for the clinical and biochemical presentation of Classic Organic Aciduria presenting as intoxication in northern areas of Pakistan.

MATERIALS AND METHODS

It was a cross sectional descriptive study conducted at Paediatrics department of Town Women & Children Hospital, Peshawar. Patients aged 0-24 months were

included in the study who fit the inclusion and exclusion criteria. Their clinical data, preliminary investigations and urinary organic acids profile were collected. The hospital has an established Laboratory where investigations like complete blood count, Blood gas analysis, serum lactate etc are done. Currently, there is no facility for diagnosis of OA in Peshawar. Analysis of urinary organic acids by sophisticated analytical methods requires expensive machinery and well-trained Laboratory technical staff, keeping in mind resource constraints of our developing countries. Due to relatively high prevalence of OA among our population of IMDs, it was decided to send urine sample for diagnosis of OA analysis using Gas Chromatography-Mass Spectrometry (GC-MS) technique at the Agha Khan Laboratory services Karachi - a regional and national centre for studies on IMDs

The present study was conducted from Aug 2018-Aug 2020. All patients who met the inclusion criteria of electrolyte imbalance, metabolic acidosis, seizures not responding to treatment, hypoglycaemia, inability to feed, apnoea, respiratory distress, family history of OAs and sibling deaths were included in the study. Those cases with congenital heart diseases, normal blood gases, known cause of disease like hypoxic insults to the brain and those responding to usual anti-epileptics were excluded. Quantitative data were given as mean (standard deviation) when normally distributed and median (interquartile range) for nonparametric data. The study was started after getting approval form of ethical committee.

RESULTS

About 36 patients with OAs were diagnosed out of 178 total number of patients. Mean age of the study population was 0.865+/- 1.07654 years and range of 1 - 2 years. About 20(53%) cases were males, while 16(47%) cases were females.

Table 1: Characteristic of patients diagnosed with Organic Aciduria

Age at diagnosis	Range=0-24 months Mean±SD=0.865+/- 1.08
Variable	N(%) out of total n=178 cases
Organic aciduria Yes	OA (MMA 3-MGA PA FA GTA MSUD) 41 (20%) 22(12%) 5(2.9%) 2(1.%) 2(1%) 10(5.6%) 2(1%)
Clinical features A Consanguinity B Poor weight gain C Developmental Delay D Family history positive for OA	 28(78%) 23(64%) 19(52%) 15(42%)
Neurological features A Generalized Hypotonia B Seizures C Abnormal reflexes D Wasting	 20(56%) 22(62%) 17(48%) 18(49%)
Biochemical findings A Hypoglycemia B Metabolic Acidosis C Ketonuria	 20(57%) 24(69%) 14(39%)

The male to female ratio in the present study was 1.1:1. Major clinical and biochemical findings included seizures, feeding difficulties, developmental delay, neurological impairment, and motor weakness, hypoglycemic and metabolic acidosis. Pattern of different OA with clinical and biochemical features is as follows in Table 1 below:

An interesting observation was found in our study regarding the frequency of patients with the high number of Methyl Malonic aciduria (22 patients), Glutaric aciduria (10 patients) and 3-Methyl Glutaconic Aciduria (5 patients) detected with a variable prevalence as compared to other studies.

DISCUSSION

In a developing country like ours, infectious diseases are more responsible for the death of a newborn, but a significant number of deaths are due to inherited metabolic disorders. Such disorders are neglected too. However, these disorders need to be investigated because many disorders are genetically acquired due to high cousin marriages in our setup.[14]Therefore, due to this reason we in our present study tried to find different Organic aciduria prevalent in our region.

Moreover, another interesting aspect that seems worth mentioning is that blood and urine specimen for screening need to be collected during a crisis of metabolic decompensation usually due to catabolic events usually preceded by vaccinations, infections or prolonged fasting. After recovery, the samples may result in decreased sensitivity and as such diagnostic abnormalities may not be detected as showed by Ali et al.[15] Our results of Northern areas are slightly different from other local studies done in Pakistan showing different prevalence of OAs[16] The study having same results in terms of consanguinity, family history and higher occurrences of MMA over other OA were authors.[17]

Additionally, the clinical condition of our patients with OA was often serious perhaps because of the late diagnosis which resulted in irreversible neurological impairment. It was obvious in patients with glutaric aciduria, in whom neural degeneration was irreversible resulting in spasticity and ataxia.[18] Clinical & Biochemical variables that were in accordance with authors [19,20]

CONCLUSION

Early diagnosis of these metabolic disorders is also important for further family planning and prenatal diagnostics. In addition, awareness of these metabolic disorders by pathologists, paediatricians, neurologists and other clinicians is also very essential. Up until NBS is established OAs should be in differential diagnosis of a sick neonate or any patient with negative sepsis screen and metabolic acidosis.

Limitations: Single centre study limits our ability to comprehend the actual burden of the disease in our set up. A public sector-based hospital would include relatively more patients from lower socio-economic conditions.

Recommendations: In future genetic studies and multi centre involvement would be highly recommended. Neurometabolic sub speciality training in Pakistan would be also a promising step in the management and diagnosis of

such disorders. A screening pilot programme would also give insight into the burden of such disorders in our region.

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