Clinical and demographic characteristics of organic acidaemias in children in a tertiary care hospital in Sri Lanka: A 4-year experience in a single centre

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Abstract

Background: Organic acidaemias (OAs) are a biochemically heterogeneous group of inborn errors of metabolism. They are rare and infrequently reported worldwide. Most OAs are clinically apparent in the neonatal period or early infancy while some can present as a chronic progressive form or even an asymptomatic form.

Objectives: To describe the clinical presentation, demographic characteristics and the incidence of OAs in Sri Lankan children.

Method: A retrospective descriptive cross-sectional study was conducted over a 4-year period by reviewing records of children suspected of having OAs referred to the Department of Chemical Pathology, Lady Ridgeway Hospital. Demographic information, clinical manifestations, biochemical investigations and mutational results were recorded and analysed using descriptive statistics. Definitive diagnosis was established by gas chromatography and mass spectroscopy (GC-MS) of urine for organic acids.

Results: Among the 458 patients suspected, 20 (4.3%) were confirmed to have an OA resulting in an incidence of 13/319,000 live births per year. The mean ages at onset of symptoms and diagnosis were 11.8 months (range; day 1 to 5 years) and 27.1 months (range; day 10 to 12 years) respectively. Among the 20 patients were 5 (25%) with propionic acidaemia and 4 (20%) with beta-ketothiolase deficiency. Nineteen (95%) presented acutely. Common manifestations were respiratory distress in 12 (60%) and persistent or recurrent vomiting in 10 (50%). Learning difficulty, dyskinesia and macrocephaly were some chronic manifestations. Biochemically, 15 (75%) had acidosis and 9 (45%) had ketosis. There were 13 (65%) deaths of which 6 were neonates with acute presentation.

Conclusions: Propionic acidaemia and beta-ketothiolase deficiency were the common OAs identified. Common clinical presentations were respiratory distress and persistent or recurrent vomiting. Acidosis was a common biochemical finding.

(Key words: Organic acidaemias, Gas chromatography /Mass spectrometry, Urine organic acid analysis, Inherited metabolic disorder)

Introduction

Organic acidaemias (OAs) or organic acid disorders are a group of inherited metabolic disorders (IMD) arising from defects in the intermediary metabolic pathways of carbohydrate, amino acids and fatty acid oxidation[1]. These disorders lead to a build-up of organic acids in tissues and their subsequent excretion in urine[2]. Most disorders are autosomal recessive in inheritance[3,4]. It is known that OAs form a very important class of IMD in critically ill children[5,6].

Most OAs are clinically apparent in the neonatal period or early infancy. The first clinical presentation may include toxic encephalopathy in acute attacks and symptoms such as poor feeding, vomiting, hypotonia, lethargy, seizures, ataxia, hepatomegaly and failure to thrive[3,5,7,8]. Patients with OAs are susceptible to metabolic decompensation during episodes of increased catabolism e.g., intercurrent illness, trauma, prolonged fasting or surgery. Some disorders can present in a chronic progressive form or even an asymptomatic form[9]. OAs are rare and infrequently reported in the western countries including the United States of America and the United Kingdom[10]. However, OAs are quite common in Asia[2]. High

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consanguinity rates among different populations have increased the prevalence of OAs[11].

The equipment and technique for gas chromatography mass spectrometry (GC-MS) analysis for urine OAs is available only in highly specialized centres and doubts have been raised about recommending this technique widely in developing countries. These procedures require expensive equipment and qualified specialists and setting up such facilities is even more difficult in developing countries since the budget for laboratory medical aid is usually low. On the other hand, effective treatment for many OAs has improved in the last decade, which makes their prompt diagnosis worthwhile[2]. Most OAs are amenable to a combination of dietary protein restriction, cofactor therapy with megavitamins and removal of toxic metabolites. In critical situations, suspicion as well as emergency treatment including metabolic stabilization will reduce mortality and morbidity.

The knowledge of the clinical presentations of OAs is important for the medical community to make a diagnosis. In Sri Lanka many OAs are undiagnosed or misdiagnosed due to lack of expensive diagnostic equipment and lack of clinical awareness. Absence of a mandatory newborn screening programme in Sri Lanka further explains the lack of data on the incidence and prevalence of OAs. To our knowledge we are presently the sole government hospital in Sri Lanka able to diagnose OAs and offer our service to the general population island-wide since 2015.

Objectives

To describe the clinical presentation, demographic characteristics and the incidence of OAs in a Sri Lankan cohort of children.

Method

A retrospective descriptive cross-sectional study was conducted over a 4-year period from June 2015 to June 2019 at Lady Ridgeway Hospital for Children (LRH), Colombo, Sri Lanka. Four-hundred and fifty-eight patients were referred from all parts of Sri Lanka to the chemical pathology department at LRH with suspected OA during the study period. The suspicion was mainly based on clinical presentation such as unexplained neurological symptoms or digestive symptoms and /or family history of an unexplained death. In addition, there were abnormal biochemical investigations which included arterial blood gas, plasma glucose, plasma lactate, plasma ammonia and urine ketones.

Medical officers reviewed medical records and collected information of all confirmed OA patients on the following aspects: age at first clinical presentation, gender, age at diagnosis, presenting clinical and biochemical features, type of OA diagnosed, consanguinity between parents, family history of unexplained death or presence of confirmed OA cases in siblings. Number of deaths was also recorded. Gaps in information were filled by a direct phone call and re-interviews with parents.

OA was confirmed by qualitative urine organic acid analysis by GC-MS (Agilent 7890B). Gas chromatography is combined with a 5977A mass spectrometer system and equipped with a split-less mode capillary injection port held at 250 °C. The column, an Agilent HP-5MS (30 m x 0.250 mm x 0.00025 mm; catalog: 19091S-433), is directly interfaced to ion source. Oven temperature is programmed from 80°C to 310°C at a rate of 6.6°C/min, and the helium flow programme is 1 ml/min. Data acquisition was done in the scan mode from m/z 50–550; the retention time and area of each peak are automatically determined and printed out by the Agilent ChemStation data analysis software. Total run time was 60 minutes. Molecule identity was obtained by interrogating the NIST database which was verified manually and followed by clinical correlation and interpretation.

Fresh random urine specimens (2-10 mL) collected with no preservatives were run on the same day when possible and the rest were stored at -30°C to be run in next batch. In addition to confirmation by GC-MS, few OA were supported by sending dried blood spots for acylcarnitine to be performed by tandem mass spectrometry (MS/MS) and for genetic studies to accredited overseas laboratories. To ensure assay validity we have joined the qualitative organic acid external quality assurance scheme conducted by the European research network for evaluation and improvement of screening, diagnosis and treatment of inherited disorders of metabolism.

Ethical issues: Approval for the study was obtained from the Ethics Review Committee of LRH (Ref No. LRH/DA/05/2017). As this was a retrospective study, written informed consent was not feasible.

Statistical analysis: Descriptive statistics were used in this study. Incidence was measured by dividing the number of diagnoses by the annual number of live births obtained from Department of Census and Statistics, Sri Lanka (the total number of live births per year was 319,000)[12].

Results

Among the 458 patients suspected of having an OA, 20 (4.3%) were confirmed with an OA resulting in an incidence of 13/319,000 live births per year. All OA were confirmed by urine organic acid analysis. Among the 20 OA additionally tandem mass spectrometry methodology and genetic studies further confirmed and supported the diagnosis in 7 and 6 cases respectively. Mean ages at onset of

symptoms and diagnosis were 11.8 months (range; day 1 to 5 years) and 27.1 months (range; day 10 to 12 years) respectively. Socio-demographic characteristics are listed in Table 1.

Among the 20 patients, propionic acidaemia was the commonest (25%) followed by beta-ketothiolase deficiency (20%). The confirmed OA subtypes are shown in table 2.

Table 1: ***Socio-demographic characteristics of organic acidaemia patients (n=20)***

Socio-demographic characteristic	Number (%)
Age	
< 1 month	07 (35.0)
> 1 month - 6 months	02 (10.0)
> 6 months -1 year	04 (20.0)
>1 year - 10 years	06 (30.0)
>10 years	01 (05.0)
Gender	
Male	09 (45.0)
Female	11 (55.0)
Ethnicity	
Sinhalese	18 (90.0)
Muslim	01 (05.0)
Tamil	01 (05.0)

Table 2: ***Frequency of organic acidaemias***

Subtype of organic acidaemia	Number (%)
Propionic acidaemia (PA)	05 (25)
Beta-ketothiolase deficiency (BKD)	04 (20)
Isovaleric acidaemia (IVA)	03 (15)
Glutaric acidaemia type 1	02 (10)
Glutaric acidaemia type 2	02 (10)
L-2-Hydroxyglutaric aciduria	01 (05)
Methylmalonic acidaemia (MMA)	01 (05)
Biotinidase deficiency	02 (10)
Total	20 (100)

The frequency of presenting symptoms and signs of OA confirmed cases are shown in Table 3. Nineteen (95%) presented acutely. Learning difficulty, dyskinesia and macrocephaly were some of the chronic manifestations. The basic biochemical abnormalities are listed in table 4.

Table 3: ***Frequency of presenting symptoms and signs of organic acidaemia confirmed cases***

Presenting symptoms and signs	Number (%)
Apnoea or respiratory distress (tachypnea)	12 (60)
Persistent or recurrent vomiting	10 (50)
Lethargy	07 (35)
Poor feeding	07 (35)
Seizures	07 (35)
Development delay	06 (30)
Failure to thrive	06 (30)
Hepatomegaly	06 (30)
Hypotonia	04 (20)
Diarrhea	04 (20)
Jaundice	03 (15)
Dehydration	02 (10)
Macrocephaly	02 (10)
Dyskinesia	02 (10)
Coma	01 (05)
Dystonia	01 (05)
Learning difficulty	01 (05)
Skin rash	01 (05)
Haematemesis	01 (05)

Table 4: ***Basic biochemical abnormalities among the organic acidaemia confirmed cases on presentation***

Biochemical abnormality	Number (%)
Acidosis	15 (75)
Ketosis	09 (45)
Lactic acidosis	04 (20)
Hyperammonemia	07 (35)
Hypoglycemia	04 (20)
Hyperglycemia	01 (05)
Elevated liver enzymes (AST/ALT)	11 (55)/03 (15)

AST: aspartate transaminase, ALT: alanine transaminase

There were 13 (65%) deaths of whom 6 were neonates with acute presentations. Family history of unexplained sibling deaths was present in 6 (30%). Consanguineous marriages were recorded in 6 (30%) cases. Table 5 summarizes the demographic and clinical features of the 20 OA confirmed cases. Table 6 shows the relative frequencies of OAs among different populations.

Table 5: ***Characteristics of the confirmed organic acidaemia patients over a four-year period***

Disorder (n)	Gender (M/F)	Parental consanguinity n (%)	Family history of sibling deaths n (%)	Mortality n (%)	Age at onset	Age at diagnosis
Propionic acidaemia (5)	2/3	03 (60.0)	03 (60.0)	05 (100.0)	3 days - 17 days	10 days - 6 months
Beta-ketothiolase deficiency (4)	3/1	0	01 (25.0)	04 (100.0)	5 months - 5.1 years	1 year - 5.2 years
Isovaleric acidaemia (3)	0/3	01 (33.3)	01 (33.3)	01 (33.3)	7 days - 5.7 years	1 month - 6.4 years
Glutaric acidaemia type 1 (2)	1/1	0	01 (50.0)	02 (100.0)	11 months - 1 year	2.2 years - 5.6 years
Glutaric acidaemia type 2 (2)	1/1	0	0	01 (50.0)	1 month - 4 months	1 month - 4 months
Methylmalonic acidaemia (1)	1/0	0	0	0	5 months	1.3 years
Biotinidase deficiency (2)	1/1	01 (100.0)	0	0	2 months - 9 months	3 months - 11 months
L-2-hydroxyglutaric aciduria (1)	1/0	01 (100.0)	0	0	3 years	12 years

Table 6: ***Relative frequencies of organic acidaemias among different populations***

Country	Study period	Number of patients	Most frequent disorder
Sri Lanka (Present study)	4 years	21	Propionic acidaemia
Jordan[20]	5 years	51	Propionic acidaemia
Saudi Arabia[21]	13 years	34	Propionic acidaemia
Libya[22]	12 years	10	Propionic acidaemia
Thailand[23]	5 years	12	Isovaleric acidaemia
India[24]	4 years	32	Propionic acidaemia
Pakistan[25]	2 years	41	Methylmalonic acidaemia

Discussion

GC-MS analysis for OA still remains the mainstay for diagnosis of OA since 1966 when Tanaka K, *et al*[13] first used GCMS to identify isovaleric acidaemia. Diagnosis of OA is expensive and this is a setback especially for developing countries where resources for diagnosing rare disorders are scarce. Hence, establishing facilities for OA detection in government hospitals of Sri Lanka should be carefully evaluated to see the cost benefit outcome.

A study has been done in our institution previously to identify OA which was diagnosed solely by sending samples to overseas laboratories[14]. That study highlighted the fact that only one third were able to undergo confirmatory testing due to lack of diagnostic facilities. Because of this fact and since most of these diseases are amenable to treatment, some effectively, we decided to set up the technique for diagnosing OA in our laboratory, currently serving as the single largest tertiary children's hospital receiving referrals island-wide. The present study is an extended and more complete study on the diagnosis and incidence of primary disorders of OA in Sri Lankan children with the setup of GC/MS in-house.

We diagnosed twenty children with OA over a period of four years. Our study found that propionic acidaemia is the most common subtype of OA in the Sri Lankan population which is consistent with studies done in Middle East and North Africa (Table 6). However, Methylmalonic acidaemia has been reported as the most common OA among different populations followed by propionic acidaemia or isovaleric acidaemia [8, 15-19].

The mean age at diagnosis of OA was 27.1 months (range; day 10 - 12 years) especially when compared to the average age of presentation (11.8 months). Studies done in Syria and Brazil showed a mean age of diagnosis 12.9 months (range 14 days – 8 years) and 23 months respectively[23,24]. This delay in diagnosis could be attributed to lack of a newborn screening programme in Sri Lanka, lack of awareness of incidence of OA among Sri Lankan pediatricians, lack of laboratories specialized in

diagnosis of these disorders in Sri Lanka, high mortality of patients affected by these diseases or a combination of these factors.

OA are rare disorders and infrequently reported worldwide[16]. In our study the incidence of OA in Sri Lanka was 13/319,000 live births. Further studies are needed to determine the actual incidence of OA. Higher prevalence is reported in Saudi Arabia (1:740), Italy (1:21422), West Midlands region in the United Kingdom (1:7962) and Canada (1:27082)[10]. Determining the incidence among Sri Lankan children with OA will help in setting the first Sri Lankan reference values and provide useful information for starting a newborn screening programme to include these treatable disorders.

The gender ratio in OA patients may differ to some extent. The male/female ratios in our study and in Thailand study were 1:1, while studies carried out in Brazil and Syria the patient populations were predominantly composed of men, with male/female ratios varying among the individual studies[8,19].

A relatively high mortality rate among OA patients was reported in our study (65%) in contrast to studies done in Syria (21.4%) and India (9.3%). We also noted there was a 100% mortality in patients diagnosed with propionic acidaemia and beta-ketothiolase deficiency. The high mortality of our patients may be possibly explained by the gap between age at presentation and age at diagnosis in our sample. Furthermore, a quarter of the patients had a family history of unexplained sibling death. All these could be attributed to several factors including paucity of information on these disorders, lack of public awareness on these disorders and their non-specific symptoms which are shared with other more common diseases such as infectious diseases[17,23].

Symptoms such as apnoea or respiratory distress, persistent or recurrent vomiting and dehydration are more likely to present in acute decompensation episodes that present in OA patients and require hospitalization and immediate management. The association of such unexplained symptoms with acidosis and or ketosis and hyperammonemia which were the most frequent biochemical findings leading to a high suspicion of OA.

There are some limitations in this study. Some patients with metabolic disorders may not have been referred to our institution due to early death before metabolic intervention. In addition, patients with a relatively mild disease may never have presented to our institute, which also contributes to the bias inherent in this study. The variability in ages at diagnosis is attributed to the delay in referring cases to the specialized centre from other hospitals, and these numbers should not reflect the expected age of presentation for the listed diseases.

The present study reveals knowledge about incidence, clinical presentations and laboratory findings of OA patients in Sri Lanka. Availability of therapy for many of these disorders appears additionally to justify the setup of such facilities despite implied extra costs. Clinical orientation is the key factor in the diagnosis of OA in light of the lack of advanced specific laboratory tests and absence of newborn screening programs. Despite the importance of these results, it is difficult to generalize the findings to the entire society. Therefore, further studies are highly recommended in order to estimate the actual incidence of OA and to assess the possibility and cost-effectiveness of applying a selective newborn screening programme of the most prevalent OAs in Sri Lanka.

Conclusions

In Sri Lankan children propionic acidaemia and beta-ketothiolase deficiency were the common OAs identified. Common clinical presentations were respiratory distress and persistent or recurrent vomiting. Acidosis was a common biochemical finding.

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