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Original research article

Organic Acidurias in Egyptian children: The urge for high-risk screening

Short title: Organic Acidurias in Egyptian children

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Abstract

Background: Organic acidurias are a group of inborn errors of metabolism with a significant diagnostic challenge and serious morbidities and mortalities. They are considered the most frequent inborn errors of metabolism among high-risk children. Gas chromatography-Mass spectrometry is a reliable diagnostic technique for organic acidurias.

This hospital-based study aimed to quantify the frequency of organic acidurias among a group of high-risk Egyptian pediatric patients, and to highlight the importance of the high-risk screening for such disorders.

Methods: One hundred fifty high-risk children presented to the inherited metabolic disease unit and the pediatric intensive care units of Cairo University Children Hospital were tested for urine organic acids using Gas chromatography-Mass spectrometry.

Results: 45/150 (30%) patients confirmed to have altered organic acids profile. Neurological manifestations were the most common presentation. Glutaric aciduria type I and Maple syrup urine disease were the most common disorders encountered among the studied group.

Conclusion: Organic acid detection by Gas chromatography-Mass spectrometry is a key to the diagnosis of many metabolic disorders. Until a national expanded newborn screening program is established, high-risk screening is highly encouraged for the early detection and proper intervention of such disorders among the Egyptian children.

Keywords:

High-risk screening. Inborn errors of metabolism. Mass spectrometry. Organic Acidurias. Pediatric intensive care unit.

Introduction

Organic acidurias (OAs) are a group of disorders resulting from enzyme deficiencies in the breakdown, pathways of amino acids, carbohydrate or β-oxidation of fatty acids metabolism[1]. OAs are characterized by increased excretion of organic acids in urine and are considered the most frequent inborn errors of metabolism (IEMs) among severely ill children[2] and one of the most prevalent IEMs in high-risk groups[3]. Despite the improvement of treatment modalities of OAs[3], the diagnosis is still difficult[4] due to the metabolic disorder episodic nature, the rarity of these disorders[5], the huge range of non-specific clinical manifestations that could be found with other common diseases[6], the unawareness of such disorders among pediatricians with different specialties, and the need for specialized investigations[5]. Diagnosis of OAs is mainly dependent on the careful interpretation of the clinical manifestations and the detection of urinary organic acids using gas chromatography-mass spectrometry (GC-MS).[7.] Specialized centers with combined professional and technical resources would help for the best of diagnosis and management.[7]

Cairo University Children's Hospital (CUCH) is the biggest pediatric referral hospital in Egypt. Through the European Union funded program for prevention, early detection and intervention in Egyptian children with genetic disability and children at risk, a selective screening study based on MS/MS technology for the detection of more than 30 types of IEMs through the analysis of acylcarnitines and aminoacids using a single dried blood spot, was started in 2006 at CUCH. Particularly, the children with clinical manifestations and specific alterations of routine lab tests or a family history suggesting a metabolic disorder were subjected to this selective screening. This program aimed to estimate the prevalence of IEMs among at-risk children to enhance the awareness among health care and community providers and to improve the registry of these disorders in Egypt. Through this program, 24/550 (4.3%) high-risk children proved to have IEMs with amino acid disorders being the most common (3.5%)

followed by OAs (0.9%).[8] Organic acids were detected in 5 cases (2 cases with Methylmalonic acidemia (MMA) and propionic acidemia (PA), 1 case with isovaleric acidemia, and 2 cases with methylcrotonyl glycinuria).[8] Afterwards, 2 similar studies conducted in the same clinic detected IEMs in 6% of high-risk children, OAs accounted for ≈ 34% of patients with MMA being the most common form of OAs.[9,10] In a third study by the same study site, 410/2934 (14%) high-risk children were diagnosed with IEMs, OAs presented 16% of IEMs with Glutaric aciduria type I (GA-I) being the most common phenotype (49%) (Unpublished data). Similar to our unpublished data, 93/308(30.2%) were confirmed to have IEMs in a recent selective study of high-risk Egyptian children with suspected IEMs using MS/MS and GA-I was the second most common detected IEM (19.4%).[11]

Many studies reported that IEMs especially OAs are common among critically ill children admitted to the emergency departments and the pediatric intensive care units (PICUs).[12-17] In a study of 139 patients with critical neurological symptoms admitted to the PICU-CUCH, non-traumatic coma presented 83% of cases with the toxic/metabolic cause accounted for 53% of cases.[18] However, the exact frequency of OAs among the PICU patients had not been previously studied.

Despite the high number of pediatric patients presenting to the IMDU and the PICUs of CUCH with the clinical suspicion of OAs, urinary organic acid profiling was not routinely performed due to limited resources.

This hospital-based study aimed to quantify the frequency of OAs among a group of high-risk children by establishing a GC-MS program through a nationally funded project. Also, it aimed to highlight the importance of the high-risk screening for such disorders among Egyptian children.

Subjects and Methods

The current 1-year study had been conducted at CUCH and involved high-risk 150 Egyptian children selected according to a stringent inclusion and exclusion criteria.

Inclusion Criteria: Patients were considered as high-risk if they had any of the following: consanguineous parents, positive family history or history of sibling death. They were further divided into two groups:

Group I: 100 children (<16 years) presented to the IMDU-CUCH with the symptoms or basic laboratory results suggestive of IEMs e.g., developmental delay, hypotonia, metabolic acidosis and hypoglycemia.

Group II: 50 critically ill children (<5 years) presented to the PICUs-CUCH in an acute state with unexplained neurological dysfunction, refractory seizures, unexplained coma, respiratory distress, or unexplained hepatic manifestations.

Exclusion Criteria: Patients with a history suggestive of ischemia, infection, perinatal hypoxia, or traumatic events and patients with other causes of metabolic acidosis (e.g., uremia).

Ethical issue: The research ethics committee of the faculty of Medicine, Cairo University approved this study (Clearance No. N-3a-2014/ Date: 8 March 2014). The procedures of the current study followed the Declaration of Helsinki.

After parental consent, the detailed history, clinical, laboratory and, radiological data of patients were obtained from patients' records with special emphasis on (A) antenatal and natal history, history of any maternal chronic illness or exposure to drug intake, feeding history, symptoms and signs suggestive of IEMs, family history including information on consanguinity, history of abortion or siblings' death, similar conditions in the same family or other genetic diseases; (B) Laboratory Investigations including complete blood count, electrolytes, arterial blood gases, anion gap, blood glucose, plasma lactate, ammonia level, C-reactive protein, liver function tests, urine ketones and reducing substances, cerebrospinal fluid testing to exclude central nervous infections, and kidney function tests; (C) Radiological

Investigations including abdominal ultrasonography (US), brain computed tomography (CT), magnetic resonance imaging (MRI) and echocardiography (ECHO) indicated. Urinary organic acid profiling was done using GC-MS (Agilent Technologies, USA).[19]

Statistical Analysis: Statistical analysis was carried out using SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA). Numerical data were expressed as median, and range and the qualitative data were presented as frequency and percentage.

Results

One hundred fifty children presented to CUCH were included in the study and underwent a metabolic workup for the potential diagnosis of OAs. All demographic, clinical, laboratory and radiological data were summarized in Supplementary Table 1. 45/150 (30%) patients confirmed to have IEMs with altered organic acids profile.

Among group I, (28/100) (28%) patients (18 males and 10 females) were found to have an altered pattern of organic acid excretion characteristic of IEMs. The median age (IQR) of patients confirmed to have specific IEM (N=28) was 13.5 months (1 month to 12 years). Consanguinity was recorded in all cases. History of abortion was encountered in 9/28 (32.1%) patients, history of siblings' death in 5/28 (17.8%) patients, and similar conditions in the same family in 11/28 (39.2%) cases. Neurological manifestations were detected in 27/28 (96.4%) patients representing the most common clinical presentation followed by gastrointestinal manifestations in 15/28 (53.5%) patients. Metabolic acidosis was the most common laboratory finding (96.4%) followed by lactic acidemia (28.5%) and atrophic brain changes were the most common radiologic finding (28.5%). The clinical, laboratory, and radiological data of the 28 patients are shown in Table I. Different phenotypes of OAs encountered in the patients and GA-I was the most common OA detected (42.8%) (Table II).

Among group II (17/50) (34%) patients (11 males and 6 females) were confirmed to have an altered pattern of organic acids excretion characteristic of IEMs. The Median (IQR) age of the

17 patients with IEMs was 4 Months (1 day - 2 years), and the majority (94.1 %) presented below the age of 1 year. Consanguinity was present in 15/17 (88.2%), and 6/17 (35.2%) had a history of sibling death. Neurological manifestations were the most common clinical manifestations where it had been found in 16/17 (94.1%) of patients followed by failure to thrive in 14/17 (82.3 %) of patients. Metabolic acidosis was the most common laboratory finding (96.1%). The clinical, laboratory, and radiological data of the 17 patients are shown in Table I. Different phenotypes of OAs encountered in the patients and maple syrup urine disease was the most common IEM detected with alteration in organic acids excretion (23%) (Table II).

Discussion

In the current study, 45/150 (30%) of the studied groups were confirmed to have altered organic acids excretion. Similar two Egyptian studies reported high detection rates of OAs among high-risk patients.[1,4] This result verifies that OAs are distinctly frequent disorders amongst the IEMs[2] particularly in the Middle Eastern populations where high consanguinity provides a genetic risk for OAs.[20] The high positive rate of OAs (34%) detected among the critically ill patients (group II) was also observed in similar Egyptian studies [14,21,22] which is higher than other PICU studies in other countries[15-17]. Such findings warrants the consideration of organic acids as a potential diagnosis in any child with any unexplained or refractory disease especially with the PICU admission.[17]

The median age of the group I patients with IEMs was 13 months. In a similar Egyptian study by El-Mesallamy et al.,[4] most of the patients presented within the 2nd year of life. This could be attributed to the delayed diagnosis caused by the unawareness about the IEMs[4] as well as the lack of specialized practitioners and healthcare centers[23]. The median age of the critically ill patients (group II) with OAs was 5 months and 88.2% presented below 1 year of age. This finding is in agreement with the fact that the severe phenotype of small molecules disorders

including OAs usually present in the first year of life.[24] None of our patients had a previous diagnosis of an IEM before presenting to the PICU confirming the episodic nature of such disorders and their common presentation as acute emergencies[17].

In the current study, high rates of consanguinity were encountered in patients with OAs. Similarly, high rates of consanguinity were reported in the other Egyptian studies[4,10,14,21,22]. This finding had been also reported in other studies in the Middle Eastern countries or countries with similar cultures and traditions[20, 21]. With the high rate of consanguineous marriage (35.3%) among Egyptians[25], providing the consanguineous couples information about the health outcomes of consanguinity became crucial.

The neurological manifestations were the most common clinical presentation among the high-risk patients with IEMs. This was in agreement with previous studies reporting that most of the IEMs usually present with neurological symptoms[3, 10, 26]. Also, Abdel Maksoud et al. reported that neurologic manifestations were common among 30 Egyptian children presented at the emergency department[12]. This finding confirms the importance of suspicion of an IEM in patients with neurologic abnormalities especially with multisystem involvement and acute symptoms[13].

Metabolic acidosis, increased anion gap, hyperammonemia, and ketosis are the characteristic findings of OAs[27]. High lactate is a common finding in OAs a result of the coenzyme A metabolism secondary interference[12]. In concordance with our findings, metabolic acidosis followed by lactic acidosis were the most common laboratory finding in patients with OAs.

GA-I was the most common organic aciduria among group I patients (43%) which is different from the selective screening studies[9, 10] done in the same clinic at CUCH, where MMA was the most common organic aciduria (~13%). However, GA-I was the second[1,28] or the third[11] most common organic aciduria subtype in other Egyptian selective screening studies. The different cut-offs used in our previous selective screening studies might explain the low detection rates

of GA-I encountered in these studies and the difference in the frequency of GA-I detected in other studies.

Despite our first pilot newborn screening (NBS) study involving 25000 Egyptian neonates didn't reveal any positive case for GA-I[9]. Shibata et al. reported that frequencies and spectra of IEMs detected by NBS differ from those identified by selective screening[29]. Also, the GA-I low excretor (LE) patients could be missed by NBS and might be at risk of poor outcome[30]. The detection of GA-I could be enhanced by the better adjustments of the glutarylcarnitine cutoff or the use of glutarylcarnitine/acylcarnitines ratios[30]. Also, urinary analysis of glutarylcarnitine -had been suggested to be added to the GA-I patients' workup especially with suggestive clinical presentations with normal plasma acylcarnitine results and without glutaric aciduria[31]. Finally, in GA-1 patients with suggestive clinical presentations must depend on enzymatic analyses and/or molecular genetic investigations[31]. Two studies investigated the genetic basis of GA-I among the Egyptian patients [32, 33] revealed a number of mutations that could be private for the Egyptian populations. This might help for the initiation of genetic based NBS program that could further improve the diagnostic sensitivity for LE patients. Early detection of GA1 is essential to minimize GA1- associated morbidity, as the clinical presentation is often not specific before the onset of encephalopathic crises[33].

Given that the pilot NBS study of IEMs involved only 3 governorates, better coverage by mandatory expanded NBS program might reveal the exact incidence and prevalence of such disorders among the Egyptian neonates. GA-I is considered a treatable disorder due to the reduction of morbidity and mortality with effective treatment, accordingly, it was included in many worldwide NBS programs[30].

Maple syrup urine disease (MSUD) was the most common detected phenotype among patients with organic acid alteration detected in the PICUs[16]. Similar to the results of the current study, MSUD was the third most common disorder in another Egyptian selective screening study[11].

Making a diagnosis of classic organic aciduria requires a high clinical suspicion and well-equipped laboratories[27]. The laboratory techniques essential for the diagnosis of metabolic diseases such as GC-MS are expensive and far off the financial ability of developing countries[14]. However, our study confirmed the importance of integration of such technologies in specialized centers to reach the diagnosis and to start prompt therapy. Lacking the molecular testing of the patients confirmed with IEMs was a limitation of the current study due to limited budget.

Finally, implementation and expansion of NBS programs is a great challenge for developing countries. In Egypt, the incidence of IEMs is 1/1944[9], however, till today, NBS is provided for only hypothyroidism and phenylketonuria.

Organic acidurias are a vast group of potentially treatable genetic metabolic disorders. This article encourages the practice of high-risk screening for such disorders as the success of treatment depends on early diagnosis and prompt institution of effective treatment to prevent the devastating neurologic complications of this group if left untreated, or if institution of treatment occurred after recurrent attacks of metabolic decompensation have produced brain damage.

Another important clinical implication of the early diagnosis of high-risk patients is the carrier detection. All asymptomatic sibs of probands diagnosed as organic aciduria should be screened by analyzing both their acyl carnitines and urine organic acids profiles, accordingly, affected asymptomatic sibs will be discovered and will be placed on treatment immediately.

Final clinical implication is that OAs should be highly suspected in PICU patients with unexplained, or refractory disease, especially if consanguinity exist in the family and patients present metabolic acidosis plus neurological symptoms. Furthermore, once the NBS program has been implemented, if the screening is

normal, an organic aciduria should not be ruled out with complete certainty, as there may be false negatives as some patients with LE GA-1.

Conclusion

Organic acid detection by GC-MS is a key to the diagnosis of many metabolic disorders and should be implemented in specialized health care centers particularly in developing countries. Until a national expanded newborn screening program is established, high-risk screening is highly encouraged for the early detection and proper intervention of such disorders among the Egyptian children.

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Disclosure

The authors declare no conflict of interest.

Authors' contributions

DAM, ZSS, LAS, MSK, HAS, EME contributed to concept and design, analysis and interpretation of data, and revised the article critically for important intellectual content.

DAM, SHE, AMA, DMA, CR, CD contributed to acquisition of data, lab work, analysis and interpretation of data, and drafting of the article.

DAM and ZSS were responsible for the funding and both contributed equally to this paper.

SHE was responsible for the final version of the manuscript.

All authors read and approved the final manuscript.

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Table 1: The clinical, laboratory and radiological data of the OAs patients (N=45).

		Group I N=28 (%)	Group II N=17 (%)
Clinical Findings	***Neurological manifestations***	***27(96.4)***	***16(94.1)***
	Developmental delay	19(67.8)	6(35.2)
	Convulsions	16(57.1)	8(47)
	Hypotonia	6(21.4)	-
	Extrapyramidal	10(35.7)	4(23.5)
	Disturbed conscious level	-	8(47)
	Gastrointestinal	***15(53.5)***	***7(41.1)***
	Recurrent vomiting	12(42.8)	5(29.4)
	Diarrhea	3(10.7)	-
	Hepatomegaly	3(10.7)	2(11.7)
	Hepatosplenomegaly	-	1(5.8)
	Failure to thrive	***12(42.8)***	***14(82.3)***
	Respiratory distress	***6(21.4)***	***13(76.4)***
	Lethargy	-	***13(76.4)***
Laboratory Findings	Metabolic acidosis	27(96.4)	16(94.1)
	Lactic acidosis	8(28.5)	13(76.4)
	Impaired Liver Functions	3(10.7)	9(52.9)
	Hyperammonemia	4(14.2)	5(29.4)
	Hypoglycemia	5(17.8)	8(*47*)
Radiological Findings	***Brain MRI (N=19/28)***		
	Atrophic changes	8(42.1)	1(20)
	Basal ganglia affection	4(21)	1(20)
	Demyelination	1(5.3)	-
	Cerebellar atrophy	-	1(20)
	Dilated ventricles	-	1(20)
	Normal	6(31.6)	1(20)
	Echocardiography (N=3/28)		
	Cardiomyopathy	1(33.3)	-
	Congenital heart disease	-	4(66.7)
	Normal	2(66.7)	2(33.3)

N: number, %: percentage, MRI: Magnetic resonance imaging, CT: Computed tomography.

Table 2: Inborn errors of metabolism detected among the studied group (N=45).

	Group I (N=28)	N (%)	Group II (N=17)	N (%)
Organic acidurias	Glutaric aciduria type I	12(42.8)	Maple syrup urine disease	4(23.6)
	Methylmalonic Aciduria	2(7.1)	Beta-ketothiolase Deficiency	3(17.6)
	Propionic Acidemia	2(7.1)	Glutaric aciduria type Ⅰ	2(11.8)
	Isovaleric Acidemia	2(7.1)	Methylmalonic Acidemia	2(11.8)
	3-methylcrotonyl-CoA carboxylase deficiency	2(7.1)	2-ketoglutaric aciduria	1(5.8)
	Multiple Carboxylase deficiency	1(3.6)		
	3-methylglutaconic aciduria	1(3.6)		
	2-ketoglutaric aciduria	1(3.6)		
	Fumaric aciduria	1(3.6)		
	Succinic semialdehyde dehydrogenase deficiency	1(3.6)		
Fatty acid oxidation defects	Medium chain acyl-CoA dehydrogenase deficiency	1(3.6)	Trifunctional protein deficiency	2(11.8)
	Very long chain acyl-CoA dehydrogenase deficiency	1(3.6)	Glutaric aciduria type Π	2(11.8)
Amino acidurias	Alkaptonuria	1(3.6)	Tyrosinemia type I	1(5.8)

Inborn errors of metabolism, N: number, %: percentage