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RESEARCH ARTICLE

Diagnosis and clinical features of organic acidemias: A hospital-based study in a single center in Damascus, Syria

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ABSTRACT

Background: Organic acidemias (OA) are a group of heterogeneous metabolic inherited disorders characterized by the accumulation of organic acids in body fluids and tissues. These are rare disorders and infrequently reported worldwide. In Syria, there is a lack of information regarding these disorders.
Objective: Our hospital-based study aimed to describe the pattern of clinical and demographic presenting features of organic acidemias among Syrian children and to shed light on the diagnostic experience of organic acidemias in the Children's Hospital of Damascus through a five year period.
Material and methods: We conducted a retrospective cohort study by reviewing the medical records of OA patients in the Children's Hospital of Damascus between 2008 and 2012. All cases were investigated by metabolic work up, including the acylcarnitine profile performed by tandem mass spectrometry (MS/MS) and quantitative urine organic acid analysis performed by gas chromatography mass spectrometry (GC-MS).
Results: A total of 70 OA confirmed cases were included in the study. There were 46 males and 31 females. Twenty-seven cases were diagnosed after the first year of life. Methylmalonic acidemia was the most frequent disorder (57.1%). There were relatively high rates of family history of unexplained death and OA confirmed cases (50%), consanguinity (74.2%) and mortality (21.4%). The most frequent symptoms were apnea or respiratory distress (65.7%) and vomiting (40%).
Conclusion: The lack of specific confirmatory diagnostic tests being performed and the high mortality and consanguinity rates among OA patients suggests

high incidence of OA in Syria. Further studies are needed to determine the actual incidence of OA and the cost-effectiveness of applying a governmental mandatory newborn screening program.

Keywords: organic acidemias, consanguinity, tandem mass spectrometry, Syria

INTRODUCTION

Organic acid disorders or organic acidemias (OA) are a group of metabolic disorders resulting from enzymatic deficiencies in the catabolic pathway of branched-chain amino acids and lysine and disorders result in accumulation of lactic acid and dicarboxylic acids, which leads to the accumulation of organic acids in the body fluids and tissues.[1,2,3] The accumulation of these toxic substances or their metabolites and lack of products of the defective pathway lead to the pathophysiology of these disorders.[4] The majority of these disorders have autosomal recessive inheritance pattern.[1,5] The affected neonate is usually normal at birth and within the first days of life.[1,6] The first clinical findings result from the toxic encephalopathy which usually arise as an acute attack within a few weeks of life with symptoms such as poor feeding, vomiting, hypotonia and lethargy.[1,6,7] In a milder form of the enzymatic deficiency, the onset of acute episodic symptoms is delayed and usually occurs within late infancy or even later, with symptom free intervals between attacks. Furthermore, these disorders can present as a chronic progressive form or even an asymptomatic form.[7] Patient prognosis can be much better with early diagnosis and treatment.[3,8]

Organic acidemias are considered the most frequent metabolic disorders among critically ill children and one of the most frequent inborn errors of metabolism among high-risk populations.[3,9,10]

Organic acidemias are rare disorders individually and infrequently reported worldwide.[11] The prevalence in British Columbia, Canada (1:27082), Italy (1:21422), and in the West Midlands, United Kingdom (1:7962), is closer to reality in comparison with Saudi Arabia (1:740), due to the high consanguinity rate among Arab populations.[12–15] In Syria, it is believed that a considerable number of OA cases are undiagnosed or misdiagnosed due to the lack of expert knowledge and trained specialists, the high cost of diagnostic tests and lack of public awareness about these disorders. The absence of mandatory newborn screening programs and the lack of scientific or statistical information on OA disorders among the Syrian population explains the unavailability of information or data on the incidence of OA and its prevalence in Syria.

The present retrospective cohort study aimed to collect clinical and demographic data on OA cases in Syrian patients and to report the diagnostic experience of OA in one medical establishment.

Table 1. Age at diagnosis for 70 organic acidemias confirmed cases.

Age at diagnosis	Number (%)
1 day – 1 month	16 (22.6%)
>1 month – 6 months	14 (20%)
>6 months – 1 year	13 (18.6%)
>1 year	27 (38.6%)

Table 2. Organic acidemias confirmed cases detected in a five year period and their characteristics.

Disorder (n)	Sex (M/F)	Consang (%)	Family history (%)	Mortalities (%)	Age at diagnosis
MMA (40)	27/13	31 (77.5)	17 (42.5)	7 (17.5)	4 days – 4 years
PA (16)	9/7	13 (81.3)	11 (68.8)	6 (37.5)	10 days – 1.7 years
BKT (5)	3/2	2 (40)	1 (20)	1 (20)	7 month – 3.5 years
IVA (4)	3/1	4 (100)	2 (50)	0	1.7 years – 8 years
HMG-CoA (2)	1/1	2 (100)	2 (100)	0	6 months – 7 months
GA-1 (1)	1/1	0 (100)	1 (100)	1 (100)	2.5 months
MGA (1)	0/1	0	1 (100)	0	10 months
HIA (1)	0/1	0	0	0	1 year

MMA: Methylmalonic acidemia; PA: Propionic acidemia; BKT: Beta-ketothiolase deficiency; IVA: Isovaleric acidemia; HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA lyase deficiency; GA-1: Glutaric acidemia type 1; MGA: 3-methylglutaconic aciduria; HIA: 3-hydroxyisobutyric aciduria.

Table 3. Results of acylcarnitine profile using MS/MS among organic acidemias confirmed cases.

Disorder (n)	MS/MS marker component
MMA	↑ C3
PA	↑ C3
	↑ C3/C2
BKT	↑ C 5OH
	↑ C5:1
IVA	↑ C5
	↑ C5/C2
GA-1	↑ C5DC
	↑ C5DC/C8
HMG-CoA	↑ C5OH
	↑ C 5OH/C3
	↑ C6DC

MMA: Methylmalonic acidemia; PA: Propionic acidemia; BKT: Beta-ketothiolase deficiency; IVA: Isovaleric acidemia; HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA lyase deficiency; GA-1: Glutaric acidemia type 1.
Note: There are no MS/MS results for the two cases with 3-methylglutaconic aciduria and 3-hydroxyisobutyric aciduria.

MATERIAL AND METHODS

A retrospective study was conducted in the Children's Hospital of Damascus, the largest specialized medical institution in Syria. Following approval of the study by the institutional ethics committee, the medical records of children diagnosed at the metabolic unit in the hospital with OA between 2008 and 2012 were reviewed.

One hundred and thirty-four patients were referred to the metabolic unit in the Children's Hospital of Damascus with suspected OA during the mentioned study period. The suspicion was based on clinical presentation such as unexplained neurological or digestive symptoms and/or positive family history of OA cases or unexplained deaths, in addition to abnormal non-specific biochemical investigations which included: serum glucose, electrolytes, serum ketone bodies, arterial blood gases, ammonia and lactate. The confirmation was carried out by advanced diagnostic biochemical metabolic work up, including the acylcarnitine profile in dry blood spots performed by tandem mass spectrometry (MS/MS) and quantitative urine organic acid analysis performed by gas chromatography mass spectrometry (GC-MS), in collaboration with private laboratories in Damascus and abroad.

The present study collected demographic and clinical data on confirmed OA cases including gender and age, consanguinity between parents, family history for unexplained death or the presence of OA confirmed cases in siblings or relatives and symptoms/clinical features. The number of mortality episodes was also recorded.

RESULTS

Out of 134 suspected OA patients, 70 patients (52.2%) underwent advanced diagnostic biochemical metabolic investigations and were diagnosed with one of the organic acids disorders, 54 cases (77.1%) were confirmed by urine organic acid analysis, and 16 cases (22.9%) were confirmed by acylcarnitine profile tandem mass spectrometry.

No advanced biochemical metabolic investigations were performed in the remaining 64 patients (47.6%)

Table 4. Results of urine organic acids analysis among organic acidemias confirmed cases.

Disorder	Increased urine organic acids
MMA	Methylmalonic, methylcitric, hydroxypropionic, 3-hydroxyisovaleric, propionylglycine
PA	Methylcitric, 3-hydroxypropionic,3-hydroxyisovaleric, 3-hydroxybutyric, 2-methyl-3-hydroxybutyric, propionylglycine
BKT	3-hydroxybutyric, 2-hydroxybutyric, 3-hydroxyisovaleric, 2-methylacetoacetic, tiglylglycine
IVA	Isovalerylglycine, 4-hydroxyvaleric, 3-hydroxyisovaleric
HMG-CoA	3-hydroxy-3-methyl-glutaric, 3-hydroxyisovaleric, 3-methylglutaconic, 3-methylcrotonyl-glycine
GA-1	Glutaric, 3-hydroxyglutaric, glutaconic
MGA	3-methylglutaconic acid, 3-methylglutaric acid
HIA	3-hydroxyisovaleric

MMA: Methylmalonic acidemia; PA: Propionic acidemia; BKT: Beta-ketothiolase deficiency; IVA: Isovaleric acidemia; HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA lyase deficiency; GA-1: Glutaric acidemia type 1; MGA: 3-methylglutaconic aciduria; HIA: 3-hydroxyisobutyric aciduria.

Table 5. Presenting signs and symptoms among 70 organic acidemias confirmed cases.

Presenting symptoms	Number (%)
Apnea or respiratory distress (tachypnea)	46 (65.7%)
Persistent or recurrent vomiting	28 (40%)
Dehydration	27 (38.6%)
Hypotonia	26 (37.1%)
Seizure	20 (28.6%)
Poor feeding/appetite loss	18 (25.7%)
Developmental delay	14 (20%)
Lethargy	14 (20%)
Diarrhea	13 (18.6%)
Failure to thrive	10 (14.3%)
Jaundice	6 (8.6%)
Ocular symptoms	4 (5.7%)
Abnormal urine odor	4 (5.7%)

to differentiate between organic acidemias and other causes of clinical manifestations as non-specific laboratory results indicated a possible metabolic disorder. Among these cases, seven were considered and treated as organic acidemias patients according to their clinical manifestation and known family history of confirmed OA cases in siblings and/or relatives, without performing any specific confirmatory tests.

Males formed 60% (n = 42) of the 70 cases, while females formed 40% (n = 28). The mean age at diagnosis was 12.9 months (range 14 days – 8 years). Table 1 shows age of diagnosis categories and the distribution of OA confirmed cases. A known family history of unexplained deaths or OA confirmed cases in siblings were found in 35 cases (50%). Parents' consanguineous marriages were registered in 52 cases (74.2%). Death occurred in 15 cases (21.4%). Three patients were discharged from the hospital on their parent's request, despite their critical situation. Table 2 summarizes the demographic and clinical features of the 70 OA confirmed cases.

Among the confirmed OA cases, there were 40 cases (57.1%) of methylmalonic acidemia (MMA) including two siblings, 16 cases (22.9%) of propionic acidemia (PA) including two siblings, five cases (7.1%) of beta-ketothiolase (BKT) deficiency, four cases (5.7%) of isovaleric acidemia (IVA) including two siblings, two cases (2.9%) of 3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMG-CoA), one case (1.4%) of glutaric acidemia type 1 (GA-1), one case (1.4%) of 3-methylglutaconic aciduria (MGA) and one case (1.4%) of 3-hydroxyisobutyric aciduria (HIA). Diagnostic markers demonstrated by MS/MS and GC-MS are shown in Table 3 and Table 4 respectively.

According to the present study, the most presented symptoms were apnea or respiratory distress (tachypnea) (65.7%), persistent or recurrent vomiting (40%) and dehydration (38.6%). The most frequent basic biochemical abnormalities were acidosis (58.6%), ketosis (47.1%) and hyperammonemia (44.3%). The presenting signs and symptoms and basic biochemical abnormalities are listed in Table 5 and Table 6 respectively.

DISCUSSION

Our study represents the first published data on the pattern, diagnosis, clinical and demographic characteristics of organic acidemias in a sample of Syrian OA patients. During the five-year period, 70 patients were diagnosed with organic acidemias at one medical establishment in Syria. Table 7 shows the number of cases of organic acidemias that were reported in our study and are similar to the number of cases reported from studies conducted in other countries. Methylmalonic acidemia is reported as the most frequent disorder in many Arab countries such as Tunisia and Lebanon, which is consistent with our findings.[16,17]

We observed a delay in diagnosis similar to that reported in Brazil and Egypt, which might be attributed to the lack of newborn screening programs in Syria.[10,18] However, the delay of diagnosis in the neonatal form, which is the most frequent form of OA, can lead to the death of the affected neonate before establishing the diagnosis. This can explain the relatively limited number of cases diagnosed at the first month of life and suggests that almost 39 percent of cases in our study have late onset presentation. This however requires further study to determine the accurate age of onset.

Table 6. Basic metabolic abnormalities detected in organic acidemias confirmed cases.

Basic biochemical abnormality	Number (%)
Acidosis	41 (58.6%)
Ketosis	33 (47.1%)
Hyperammonemia	31 (44.3%)
Lactic acidosis	23 (32.9%)
Hyperglycemia	13 (18.6%)
Hypoglycemia	9 (12.9%)

Table 7. Relative frequencies of organic acidemias among different populations.

Country	Duration of the study	No. of patients	Most frequent disorder
Present study	5 years	70	MMA
India[11]	4 years	30	PA
Tunisia[16]	23 years	158	MMA
Lebanon[17]	12 years	83	MMA
Libya[20]	12 years	10	MMA-PA
Jordan[21]	5 years	51	PA
Thailand[22]	5 years	5	MMA-IVA

MMA: Methylmalonic acidemia; PA: Propionic acidemia; IVA: Isovaleric acidemia.

It is known that consanguinity between parents can increase the chance of offspring being affected by autosomal recessive disorders in general, including organic acidemias. These chances can be maximized especially in the case of positive family history of such diseases.[18] High rates of parental consanguinity and positive family history among OA patients were reported in our study and in Egypt.[19]

The relatively high mortality rate among OA patients that was reported in our study could be attributed to several factors including the lack of public awareness about OA, the paucity of information on these disorders, their non-specific symptoms which are shared with other more common diseases such as infectious diseases, and the shortage of experienced physicians in the domain of metabolic disorders in general. These factors lead to the exclusion of OA from the differential diagnosis which results in delayed diagnosis, treatment and consequent death.

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

The estimation of the diagnosis was the major difficulty in dealing with these disorders due to the lack of confirmatory tests for financial reasons, in addition to the absence of mass or selective newborn screening program. In some cases, the patients died before the required tests were performed.

CONCLUSION

This study suggests that the clinical orientation is still the key factor in the diagnosis of these diseases 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 organic acid disorders and to assess the possibility, interest and cost-effectiveness of applying a selective newborn screening program of the most prevalent organic acid disorders within Syria.

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