ORGANIC ACIDEMIA IN JORDAN: AN EXPERIENCE FROM QUEEN RANIA AL ABDULLAH HOSPITAL FOR CHILDREN

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ABSTRACT

Background: Organic acidemias are inborn metabolic errors resulting from enzyme or transporter defects in breaking down amino acids, fatty acids, or carbohydrates. This leads to accumulating unusual and potentially harmful organic acids, excreted in urine. This study aimed to establish a database, enhance clinical understanding of organic acidemias in Jordan, and compare regional findings.

Method: This retrospective study was conducted at Queen Rania Al Abdullah Hospital for Children between 2010 and 2023 and analyzed patients with organic acidemias, considering sociodemographic features, clinical and laboratory results, familial history, and parental consanguinity.

Results: The study involved 73 patients, with males comprising 53.4%, and the median age at presentation was 12 months. Approximately 30.1% had a positive family history, and 78.1% had parental consanguinity. The mortality rate was 11%. Isovaleric acidemia (IVA) was the most common type (28.8%), followed by 3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMG-CoA) (20.5%) and methylmalonic acidurias (MMA) (19.2%). Patients with propionic acidemia (PA) presented at a younger age, while those with glutaric acidemia (GA) were the oldest. Despite subtype variations, no significant differences were found in age, sex, family history, consanguinity, or mortality.

Conclusions: Isovaleric acidemia was identified as the most common type among organic acidemias. Detecting these conditions presents challenges and delays, underscoring the urgent need for newborn screening for early intervention. Additionally, healthcare professionals must recognize the clinical symptoms and interpret biochemical test results associated with these disorders.

Keywords: Organic acidemia, Acidurias, Inborn error of metabolism, Jordan.

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INTRODUCTION

Metabolic disorders result from an enzyme or a transporter defect in the catabolic pathway Organic acidemias (OA), also termed organic acidurias, constitute a group of inborn errors of of the aminoacids (AA), fatty acids (FA), or carbohydrates [1]. These deficiencies lead to accumulating unusual and often harmful organic acid byproducts and an augmented excretion of these acids through urine [2]. More than 65 defects were identified in these pathways [3].

Most organic acidemias are evident during the newborn period or early infancy, although less severe variations might only become apparent during adolescence and adulthood or possibly elude medical detection entirely [4].

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OAs are classified as disorders of intoxication as the accumulation of an organic acid in body fluids affects other pathways that lead to further build-up of unwarranted substances like lactic acid and ketone bodies. Consequently, several body systems, such as the central nervous system, heart, liver, gastrointestinal tract, kidneys, and musculoskeletal systems may all be affected [5].

OAs are also classified as systemic OAs, ketogenic/ketolytic OAs, and cerebral OAs [6]. Systemic OAs usually present with wide anion gap metabolic acidosis with or without hyperammonemia, including propionic acidemia (PA), methylmalonic acidurias (MMA), isovaleric aciduria (IVA), and several others. The ketogenic/ketolytic organic acidemias, such as 3-hydoxy-3-methylglutaryl-CoA lyase deficiency (HMG-CoA), can present with hypoglycemia and occasionally hyperammonemia. Cerebral OAs, such as glutaric aciduria 1 (GA1), usually present with developmental delay and seizure disorders [1,6].

Children afflicted by these conditions experience a critical episode of life-threatening metabolic acidosis, which can be misidentified as sepsis, carrying a substantial risk of mortality if not correctly diagnosed. Metabolic decompensation can arise during heightened catabolism, such as concurrent illnesses, injuries, surgeries, or extended fasting periods [7].

Early diagnosis can be achieved by screening the acylcarnitines of dry blood samples via tandem mass spectrometry at 48-69 hours. Aminoacids chromatography and organic acids chromatography are also used in the basic metabolic screening programs [8]. New methods are developed for rapid screening for OAs as rapid management is vital. On the other hand, an enzymatic assay of the deficient enzyme and a genetic assay of the defective gene is mandatory to confirm the diagnosis [9, 10].

Management of OAs after stabilizing the patient focuses on removing the accumulated organic acid, preventing further catabolism to ensure less accumulated toxin and to provide the body with energy. Furthermore, eliminating the accumulating toxin, replacement of non-produced products, and managing long-term complications [11]. When known, cofactor supplements to the affected deficient enzyme are also given to enhance its residual activity to the upper level [12]. Liver and combined liver/kidney transplantations are promising tools to manage OAs or decrease acute decompensation states [13]. Enzyme replacement therapy and gene therapy are also in progress [14].

This study aimed to review organic acidemia in Jordan to form a database for future studies, to increase the knowledge of clinical features and outcomes in these patients, and to compare our results with regional ones.

METHODS

management is vital. On the other hand, an enzymatic assay of the deficient enzyme and In this retrospective single-center study, we reviewed all patients treated for organic acidemia at Queen Rania Al Abdullah Hospital for Children (QRHC), from 2010 to 2023. QRHC is an integrated hospital of King Hussein Medical City (KHMC) in Amman, and the metabolic unit is a referral center for metabolic disorders from all districts of the kingdom. a genetic assay of the defective gene is mandatory to confirm the diagnosis [9, 10].

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (version 23.0, SPSS Inc., Chicago, IL, USA). Descriptive statistics were utilized to describe the characteristics of the study sample and present continuous data (median, frequency, and percentages). The Kolmogorov-Smirnov Test was used to assess data normality.

The exploration of differences among organic acidemia subtypes was conducted using the chi-square test and fisher exact test as appropriate. Additionally, Kruskal-Wallis test along with pairwise test to assess the relationship between the diagnosis and age was employed to compare means between groups. The statistical significance of the results was determined by applying a 95% confidence interval ($P < .05$).

RESULTS

Data were analyzed using the Statistical Package for the Social Sciences (version 23.0, SPSS Inc., Chicago, IL, USA). Descriptive statistics were utilized to describe the characteristics of the study sample and present continuous data (median, frequency, and percentages). The Kolmogorov-Smirnov Test was used to assess data normality.

The exploration of differences among organic acidemia subtypes was conducted using the chi-square test and fisher exact test as appropriate. This review included seventy-three patients, with males representing 53.4%. The Median age of patients at the time of the study was 6.79 years. The median age at the diagnosis or presentation was 12 months. Around a third of patients (22, 30.1%) have a positive family history, and 78% of patients their parents are relatives.

Mortality accounted for 11% of all patients (8 patients). In our study, IVA was the most common type, accounting for 28.8% (21 patients), followed by HMG-CoA and MMA, which represented 20.5% (15) and 19.2% (14) of cases, respectively,

Additionally, Kruskal-Wallis test along with pairwise test to assess the relationship between the diagnosis and age was employed to compare means between groups. The statistical significance of the results was determined by applying a 95% confidence interval ($P < .05$).

Pairwise comparisons of diagnoses using the Bonferroni post hoc test revealed several significant differences in the median age at diagnosis (months). HMG-CoA exhibits a significant distinction from IVA ($p = 0.000$) and GA ($p = 0.005$). PA also shows a significant difference compared to IVA ($p = 0.005$). Additionally, MMA differs significantly from IVA ($p = 0.014$). These significant differences, observed at a significance level of 0.05, indicate notable variations in the studied conditions.

Furthermore, a thorough analysis of subgroups revealed no statistically significant differences in various parameters. These encompassed age at the time of the study, gender distribution, family history, parental consanguinity, and mortality rates. This suggests that, despite the differences in age of symptom presentation among PA, HMC-CoA, IVA, and GA, other demographic and clinical characteristics remained relatively consistent among the subgroups. This information contributes to a more nuanced understanding of the patient population and aids in the broader comprehension of these metabolic disorders.

Table 2 illustrates the initial presentation at the time of diagnosis or referral to our metabolic clinic. The most common symptom was vomiting and refusing food (63%), with metabolic acidosis (68.5%) and hypoglycemia (58.9%) being the prevailing findings. Hyperammonemia was present in approximately half of the patients, and failure to thrive was reported in about a third of the cases. Encephalopathy and hypotonia were
reported in 42.5% and 41.1% of cases, respectively.

Examining the main findings for each presentation of organic acidemia subtypes, IVA predominantly manifested as acidosis with a wide anion gap and hyperammonemia. HMG-CoA's primary presentation included acidosis, hyperammonemia, hypoglycemia, and vomiting. Hypoglycemia was the main presentation in MMA. PA's most predominant findings were hypoglycemia and developmental delay, whereas in GA, the leading presentation comprised hypoglycemia, vomiting, hypotonia, and developmental delay.

Table 1: Descriptive Analysis of Organic Acidemia Subtypes.

	Total	MMA	PA	IVA	HMG-CoA	GA	P- value
Number of patients (%)	73 (100)	14 (19.2)	12 (16.4)	21 (28.8)	15 (20.5)	11 (15.1)	
Median age at study (years)	6.795	12	3.25	5.875	6	7	0.122
Median age at diagnosis (months)	12	9	7	27	6	24	<0.05
Sex							
Male	39 (53.4)	7 (50)	7 (58.3)	10 (47.6)	10 (66.7)	5 (45.5)	0.772
Female	34 (46.6)	7 (50)	5 (41.7)	11 (52.4)	5 (33.3)	6 (54.5)	
Positive family history N (%)	22 (30.1)	5 (35.7)	5 (41.7)	5 (23.8)	6 (40)	1 (9.1)	0.246
Parental consanguinity							
Non-relative	16 (21.9)	2 (14.3)	2 (16.7)	6 (28.6)	3 (20)	3 (27.3)	0.496
First cousin	46 (63)	11 (78.6)	7 (58.3)	12 (57.1)	9 (60)	7 (63.6)	
Second cousin	6 (8.2)	0	2 (16.7)	3 (14.3)	0	1 (9.1)	
Third cousin	5 (6.8)	1 (7.1)	1 (8.3)	0	3 (20)	0	
Mortality	8 (11)	2 (14.3)	5 (41.7)	1 (4.8)	0	0	0.89

MMA: Methylmalonic acidemia; PA: Propionic acidemia; IVA: Isovaleric acidemia; HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA lyase deficiency; GA-1: Glutaric acidemia type 1.

Table 2: Presentation of Organic Acidemia Subtypes.

Organic acidemia subtype	Total n=73	MMA n=14	PA n=12	IVA n=21	HMG-CoA n=15	GA n=11	P-value
Hyperammonemia	38 (52.1)	3 (21.4)	6 (50)	15 (71.4)	11 (73.3)	3 (27.3)	0.008
Hypoglycemia	43 (58.9)	10 (71.4)	9 (75)	3 (14.3)	12 (80)	9 (81.8)	<0.005
Acidosis	50 (68.5)	3 (21.4)	10 (83.3)	17 (81)	13 (86.7)	7 (63.6)	0.001
Failure to thrive	27 (37)	6 (42.9)	8 (66.7)	4 (19)	2 (13.3)	7 (63.6)	0.006
Encephalopathy	31 (42.5)	8 (57.1)	8 (66.7)	7 (33.3)	5 (33.3)	3 (27.3)	0.173
Vomiting and refusing food	46 (63)	5 (35.7)	7 (58.3)	12 (57.1)	13 (86.7)	9 (81.8)	0.038
Hypotonia	30 (41.1)	5 (35.7)	8 (66.7)	3 (14.3)	5 (33.3)	9 (81.8)	0.002
Developmental delay	32 (43.8)	5 (35.7)	10 (83.3)	5 (23.8)	3 (20)	9 (81.8)	<0.005

MMA: Methylmalonic acidemia; PA: Propionic acidemia; IVA: Isovaleric acidemia; HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA lyase deficiency; GA-1: Glutaric acidemia type 1.

DISCUSSION

Queen Rania Al Abdullah Hospital for Children (QRHC) is an integrated hospital of King Hussein Medical City in Amman, the capital of Jordan. It is a specialized referral center for all districts of the kingdom, including metabolic diseases. Metabolic diseases are rare and require specialized treatment, which is unavailable in most district hospitals. Therefore, most metabolic diseases are referred to our units, making the studies from the metabolic unit at QRHC representative for Jordan.

The exact incidence of metabolic diseases is unknown in Jordan. However, secondary to high consanguineous marriage, such conditions are expected to be high. Thus, more studies are required to understand the prevalence of metabolic diseases, including organic acidemia in Jordan. Therefore, we can establish a base for future studies and even set a screening program for metabolic disease accordingly.

In one study from Jordan published in 2012, 212 patients with metabolic disorders treated at a metabolic clinic at KHMC over five years (2005 – 2010) were reviewed to study the distribution of inborn errors of metabolism. OA represented 24.1% of all metabolic patients, and PA was the most common type, followed by MMA, 27.5% and 11.8% within the same category. Nevertheless, in twenty-nine patients, the exact type was undetermined. However, they presented with acidotic breathing with or without encephalopathy, and their blood gases showed wide anion gap metabolic acidosis, high ammonia, and lactate. Nevertheless, the samples for specific diagnoses, such as organic acid chromatography in urine, were mostly sent. Yet, the exact diagnosis was not made, and those patients received supportive treatment according to their symptoms [15].

In our review, IVA was the most common type, followed by HMG-CoA and MMA. In contrast, PA, the most common type in the previously published study, came forth in frequency in the current study; this may be attributed to the fact that 56.9% of the organic acidemia subtype was undiagnosed.

In one regional study from Syria [16], a border country to Jordan with similar population sociodemographic characteristics, seventy patients with OA were reviewed. The mean age at diagnosis was 12.9 months, while in our study, the mean age at presentation was 20.5 months; this can be explained by the fact that our unit is a referral center from all the districts of Jordan, and many of those patients received local treatment at their local hospital before referral which contributed to older ages at diagnosis. The family history in the Syrian study was found in half of the patients compared to a third of the patients in our review. Parental consanguineous marriages were registered in 74.2% of patients, near our findings of 78.9%. Mortality was higher in the Syrian study, 21.4% compared to 11% of our patients. Additionally, the frequency of subtypes was as follows: MMA was the most common type and accounted for 57.1 % of cases, followed by PA, which accounted for 22.9%.

In another study from Lebanon [17] over 12 years (2008 – 2010), out of 83 patients diagnosed with OA, MMA was the most common type and accounted for 27.7%. Similarly, MMA was the most prevalent type in Tunisia, accounting for 33.5% [18] and 24.4% in Italy [19]. Moreover, PA was

the most common type in Oman at 44.4% [20]. In the Arabic world, secondary to high consanguineous marriage and the absence of neonatal screening for metabolic diseases, the prevalence of such diseases is expected to be high [21].

OA can be presented in newborns and infancy as irritability, lethargy, vomiting, seizures, decreased level of consciousness, and death [2, 7-10]. Additionally, it can mimic a sepsis-like picture [22]. Therefore, this explains the older age of patients at the presentation at our unit because those patients received primary treatment at the district hospitals in Jordan. Thus, the diagnosis is delayed due to confusing presentation and the absence of a screening program for OA in Jordan. According to Unsal Y. et al., 80% of admissions to the neonatal intensive care unit (NICU) of newborns with IEM were due to OAs with increased mortality in the presence of wide anion gap metabolic acidosis and hyperammonemia [5].

The neonatal onset of PA is characterized by severe symptoms like ketoacidosis and seizures, often resulting in death [23]. In our review, PA mortality was 41.7%. However, late-onset chronic intermittent PA is marked by recurrent ketoacidosis episodes, developmental regression, and neurological issues like movement disorders. PA has a worse prognosis than IVA or MMA due to cardiac complications, and late complications encompass pancreatitis, anorexia, dermatitis, hearing loss, and chronic intellectual disability [24].

Early neonatal diagnosis significantly improves outcomes; for example, 62% of IVA patients achieve normal or near-normal neurocognitive functioning [25]. This signifies the importance of screening programs for IEM. Therefore, treatment can be started early and consequently minimize the complications. We believe many unexplained neonatal deaths are secondary to OA, which explains the relatively limited number of cases diagnosed in the first month of life. Additionally, due to the absence of a screening program, physicians should be aware of clinical presentation and biochemical analysis of OAs and other IEMs.

There are certain constraints within our study that we should acknowledge. The absence of comprehensive clinical documentation poses challenges to a thorough analysis of our findings. Moreover, we believe many patients might not have been referred to our facility due to early mortality in the neonatal or infancy stages, while others may have sought treatment locally. Consequently, we expect that the actual prevalence of OA is considerably greater than our study indicates. We advocate for integrating OAs into national screening programs to enhance affected individuals' well-being and care outcomes.

Several recommendations for future research are evident based on the study's findings. First, conducting comprehensive investigations into specific subtypes of OAs is crucial to elucidate their genetic foundations, clinical manifestations, and treatment responses. Such studies should ideally involve multiple centers to enhance sample size and the robustness of data. Second, implementing pilot studies to evaluate the feasibility and cost-effectiveness of nationwide newborn screening programs for OAs in Jordan is recommended. These studies should assess the long-term benefits of early detection and intervention on patient outcomes. Finally, longitudinal studies tracking

patients diagnosed with OAs from infancy into adulthood are necessary to understand the long-term outcomes and complications associated with these disorders. This research would provide valuable data on the effectiveness of current management strategies and identify areas needing improvement.

CONCLUSION

In our study, IVA was the most prevalent among OAs. Given the challenges and time delays associated with diagnosing these conditions, there is a strong endorsement for implementing newborn screening as a crucial step for early intervention and guidance. Additionally, healthcare professionals need to be well-versed in the clinical manifestations of these disorders and proficient in interpreting biochemical test results.

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