Study of biochemical and hematological parameters of propionic academia patients at Tripoli Childrens Hospital - Libya

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الملخص بالعربي

الخلفية: مرض حموضة البروبيونيك خلل وراثي نادر يحدث نتيجة لنقص في إنزيم البروبيونيل كوإنزيم أ كاربوكسيليز. (PCC) يتسبب هذا الخلل في احمضاض الدم لعملية أيض الأحماض الأمينية ذات السلسلة المتفرعة، ويتفاوت مدى انتشاره في المجتمعات السكانية.

الهدف: هدفت هذه الدراسة إلى تحديد تأثير الجنس والتاريخ العائلي للمرض على مختلف المؤشرات الكيمياء الحيوية والدموية والهيماتولوجية ل 25 مريضًا يعانون من أعراض حموضة البروبيونيك خلال الفترة الممتدة من 2011 وحتى 2022.

النتائج: أوضحت النتائج عدم وجود اختلافات ذات دلالة إحصائية بين الجنسين في مستويات الامونيا واليوريا والكوليسترول والدهون الثلاثية وانزيمات الكبد وكذلك مستويات الهيموجلوبين وكريات الدم البيضاء وصفائح الدم. في حين اظهرت النتائج وجود اختلافات احصائية معنوية في مستوي امونيا الدم وتوازن حموضة الدم المرتبطة بالتاريخ العائلي المرتبطة بالتاريخ العائلي للمريض من عدمه حيث كانت (p= 0.005، p= 0.04) على التوالي، بينما لم تظهر المؤشرات الأخرى اختلافات ذات دلالة إحصائية بناءً على التاريخ العائلي للمرض. كما اظهر توزيع الحالات استنادًا إلى تاريخ التشخيص أن غالبية الحالات (36%) تم تشخيصها بين عامي 2014 و2016. عند

توزيع الحالات على حسب قرابة الزوجين من عدمه كانت (64%) من الأطفال المصابين لأبوين ذوي قرابة مما يشير الي ارتباط محتمل بين زواج الاقارب ومرض حموضة البروبيونيك.

الاستنتاج: تشير هذه الدراسة إلى أن الجنس لم يكن له تأثير ملحوظ على المعايير المقاسة، إلا أن التاريخ العائلي كان مرتبطًا بارتفاع مستويات الأمونيا وتوازن الحموضة والقاعدة. تتوقع الدراسة الحالية وجود علاقة بين زواج الاقارب والعوامل الموروثة لمرض حموضة البروبيونيك.

ABSTRACT

Background: Propionic acidemia (PA) is an autosomal-recessive inborn error of metabolism resulting from a deficiency in propionyl coenzyme A carboxylase (PCC). It disrupts the metabolism of branched-chain amino acids and exhibits variable prevalence across different populations and geographic regions.

Objective: This retrospective study aimed to investigate the effect of sex and family history on clinical characteristics and metabolic profiles of PA among children at Tripoli Children's Hospital, Libya from 2011 to 2022.

Methodology: The methodology involved conducting a retrospective study of 25 patients who presented symptoms of PA and Tripoli Children Hospital admission from 2011 to 2022.

Results: This retrospective research investigated potential gender-based differences and the impact of family history on various health parameters within 25 patients displaying symptoms of PA. Analysis of gender-based differences showed There is no statistically significant variations in cholesterol, triglycerides, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), bilirubin, white blood cell count (WBC), hemoglobin (Hb), and platelet (PLT) levels. However, significant differences were observed in ammonia levels and

arterial blood pH associated with family history (p = 0.005, p = 0.04), while other parameters did not exhibit significant variations based on family history. Additionally, the distribution of cases based on the diagnosis date revealed that the majority of cases (36%) were diagnosed between the years 2014 and 2016. Furthermore, 64% of the cases were born to consanguineous couples, suggesting a potential association between consanguinity and the development of PA.

Conclusion: This research highlights the effect of sex, family history and consanguineous couples on some biochemical and hematological parameters among PA patients. Although sex had no significant impact on the measured parameters, the family history was associated with elevated ammonia levels and acid-base balance. The present study expects the relationship between consanguineous marriage and the inherited factors of PA.

Keywords: Propionic acidemia, Metabolism, Propionyl coenzyme A carboxylase

Abbreviation List:

Alanine Transaminase: ALT

Alkaline Phosphatase: ALP

Arterial Blood Gas: ABG

Aspartate Transaminase: AST

Chorionic Villus Sampling: CVS

Hemoglobin: Hb

Platelet: PLT

Potassium: K

Propionic Academia: PA

Propionyl Coenzyme A Carboxylase: PCC

Propionyl-CoA Carboxylase Subunit Alpha: PCCA

Propionyl-CoA Carboxylase Subunit Beta: PCCB

Power of Carbon Dioxide: PCO2

Power of Carbon Trioxide: PCO3

Power of Hydrogen: PH

Power of Oxygen: PO

Sodium: Na

Statistical Package for the Social Sciences: SPSS

White blood cell: WBC

1. INTRODUCTION:

The estimated incidence of propionic acidemia in the United States is 1:105,000–130,000 people, the highest among the Amish populations[1,2,3]. The incidence is highest in the Inuit of Greenland—1:1,000[1,4] and next highest is in some Saudi Arabian populations—1:2,000- 28,000 [1,5,6]. The true prevalence may be higher because undocumented acidopathies may cause many neonatal deaths.

PA is caused by a lack of propionyl-CoA carboxylase, a mitochondrial multimeric enzyme that catalyzes the conversion of propionyl-CoA to D-methylmalonyl-CoA [7]. PA is caused by alterations in the PCCA and PCCB genes, which result in a lack of the enzyme propionyl-CoA carboxylase. The amino acids isoleucine, valine, threonine, and methionine require this enzyme for efficient breakdown [8]. These amino acids are required for

optimal development and growth. Propionyl-CoA carboxylase also breaks down cholesterol, some fatty acids, and other chemicals (metabolites) required for metabolic actions or processes [9]. Propionyl-CoA carboxylase deficiency leads to the accumulation of toxic chemicals (metabolites).

The concentration of specific metabolites in amniotic fluid or the activity of the propionyl-CoA carboxylase enzyme in fluid or tissue samples collected from the fetus or uterus during pregnancy (amniocentesis or chorionic villus sampling [CVS]) can also be used to determine the diagnosis [10]. A sample of the fluid surrounding the growing embryo is extracted and examined during amniocentesis. CVS entails removing and examining tissue from a section of the placenta [11]. The majority of individuals with this medical problem present in the newborn period with severe metabolic acidosis and hyperammonemia [12]. Later presentations with mostly neurological symptoms, as well as asymptomatic individuals, have been recorded. PA is classified clinically into two subtypes: early-onset and late-onset PA [13]. The great majority of patients with early-onset illness are full-term newborns with unremarkable Apgar scores. One-quarter of patients may have a family history of an unexplained death of a sibling or a sibling who has been diagnosed with PA [14]. A history of consanguinity may exist, as with any autosomal recessive illness. Early-onset illness is frequently more severe and manifests as hypotonia, lethargy, vomiting, feeding difficulties, and tachypnea during the first weeks of life, but as late as three months [15]. Seizures, hepatomegaly, diarrhea, constipation, coma, apnea, and hypothermia are the less prevalent signs and symptoms [16]. Acute decompensation is characterized by episodes of ketoacidosis

and/or hyperammonemia, which commonly begin in childhood. In one series, the median age of presentation for the late-onset variant of PA was 16 months. Patients may present as early as 3 - 6 months after birth, but they may not present until they are far into adulthood [17]. Late-onset forms are also more frequently associated with unusual presentations characterized by a wide range of signs and symptoms. Hematological abnormalities such as anemia, neutropenia, thrombocytopenia, or pancytopenia were the most prevalent complications in our patients, as previously documented [18].

2. METHODOLOGY:

The methodology involved conducting a retrospective study of 25 patients who presented symptoms of PA and Tripoli Children Hospital admission from 2011 to 2022. The research data were extracted from medical records of children who were diagnosed with PA and underwent follow-up at Tripoli Children's Hospital in Libya. The results were statistically analyzed using SPSS software (version 25) to examine the relationship between variables. A p-value of <0.05 was considered to be a statistically significant.

3. RESULTS:

This retrospective study investigates the impact of gender and family history on clinical features and metabolic profiles in cases of PA among a sample of 25 pediatric patients at Tripoli Children's Hospital in Libya between the years 2011 and 2022.

Parameter	Male (No.12) mean±SD	Female (No.13) mean±SD	"t-Test" p. value
Ammonia (mcg/dl)	80.86±35.653	106.92±47.656	0.259
Total Protein (g/dl)	5.121±0.9639	5.773±.0.8603	0.988
Albumin (mg/dl)	3.34±0.9507	3.420±0.8753	0.622
Urea (mg/dl)	45.13 ± 29.926	28.67 ± 12.521	0.254
Creatinine (mg/dl)	0.375±0.1165	0.467± 0.1371	0..614
Phosphor (mg/dl)	5.325±0.1626	5.046±1.6268	0.146
Na (meq/L)	138.98 ± 7.33	136.09 ± 6.604	0.598
K (meq/L)	4.725 ± 0.9425	4.3275 ± 0.70204	0.630
Calcium (mg/dl)	9.294 ± 1.5489	8.159 ± 3.0419	0.173
Vitamin D (ng/ml)	24.45 ± 16.03008	21.64 ± 16.08958	0..953
Sugar (mg/dl)	79 ± 20.386	101.67 ± 66.061	0.473
ABG-PH	7.348± 0.13971	7.327±0.19032	0.216
ABG-PCO3 mmol/L	16.9±4.4989	16.567 ± 6.2192	0.659
ABG- PO mmHg	134.5 ± 46.119	85.9 ± 35.97	0.468
ABG-PCO2 mmHg	28.56 ± 6.149	24.25 ± 5.189	0.892
Cholesterol (mg/dl)	103.5 ± 39.543	126.14 ± 26.829	0.294
Triglyceride (mg/dl)	127 ± 68.372	91.57 ± 47.021	0.131
ALT (U/l)	26.11 ± 9.203	22.33 ± 11.180	0.335
AST (U/l)	49.94 ± 16.239	31.78 ± 15.098	0.401
ALP (U/l)	260.56± 230.5	246.4±115.194	0.360
Direct. Bilirubin (mg/dl)	0.272 ± 0.2047	0.145± 0.0782	0.092
Total Bilirubin (mg/dl)	0.56 ± 0.5299	0.335 ± 0.2286	0.164
WBC ($\times 10^3/\mu l$)	10.888 ± 4.9409	8.862 ± 3.6409	0.633
Hb (g/dl)	8.45 ± 2.2032	10.131 ± 1.6064	0.285
PLT ($\times 10^3/\mu l$)	366.5 ± 155.01	425.9 ± 167.616	0.573

Table 1: Effect of gender on some biochemical and hematological parameters of PA patients

This table compares various parameters between males and females, including mean values with standard deviations and

corresponding p-values. Ammonia levels showed a slight difference between males and females, with males having a lower mean level than females. However, this difference was not statistically significant for ammonia (p = 0.259), and total protein levels were not significant p-value >0.05.

Albumin levels, an essential indicator of liver function, were also a non-significant difference between males and females (p-value of 0.622). On the other hand, urea levels showed a notable difference between males and females. Males had a higher mean urea level than females, although the p-value of 0.254 suggests that, the difference was not statistically significant. Furthermore, creatinine levels, which reflect kidney function, were not shown a significant difference between males and females, with a p-value of 0.614.

Phosphor levels demonstrated no significant difference between males and females, with males having a slightly higher mean than female cases. Sodium (Na) levels were not different substantially between males and females. The p-value of 0.598. Similarly, potassium (K) levels were not significantly different between males and females.

Calcium levels also exhibited a slight difference between males (9.294±1.5489) and females (8.159±3.0419), but this difference was not statistically significant (p-value = 0.173). Similarly, no significant sex-based differences were observed in vitamin D levels (p-value = 0.953). Sugar levels showed a slight difference between males and females, although the p-value of 0.473 suggested that the difference was not statistically significant. Regarding arterial blood gas parameters, including pH, PCO3, PO, and PCO2, none demonstrated a significant difference between males and females. The p-values >0,05.

The study revealed no significant differences in cholesterol and triglyceride among males and females. Similarly, ALT, AST, and ALP were shown no significant differences among sex-based.

Bilirubin (direct and total): The present study identified no significant sex-related differences in direct or total bilirubin levels.

White Blood Cell Count (WBC) and Hemoglobin (Hb): The analysis revealed no significant differences between males and females in WBC counts and Hb levels. Similarly, no significant sex-based difference in PLT counts, with females exhibiting higher levels than males.

Table 2: Effect of Family History on the Various Parameters among PA.

Parameter	family history of Propionic acidemia (No.18) mean±SD	No family history of Propionic acidemia (No.7) mean±SD	"t-Test" p. value
Ammonia (mcg/dl)	107.78 ± 29.89	82 ± 14.024	0.005*
Total Protein (g/dl)	5.441 ± 1.08	5.127 ± 0.7154	0.051
Albumin (mg/dl)	3.314 ± 0.7814	3.572 ± 1.2223	0.148
Urea (mg/dl)	36 ± 24.243	32.25 ± 12.01	0.476
Creatinine (mg/dl)	0.425 ± 0.1	0.45 ± 0.2517	0.047*
Phosphor (mg/dl)	5.064 ± 1.6307	5.255 ± 0.0636	0.115
Na (meq/L)	138 ± 6.767	134.23 ± 7.377	0.805
K (meq/L)	4.3806 ± 0.63225	4.91 ± 1.35465	0.052
Calcium (mg/dl)	8.418 ± 2.7743	9.25 ± 1.7805	0.456
Vitamin D (ng/ml)	20.5686 ± 13.5466	26.325 ± 19.6539	0.459
Sugar (mg/dl)	99.38 ± 64.473	80.4 ± 15.453	0.422
ABG-PH	7.3119± 0.12128	7.4389± 0.06139	0.040*
ABG-PCO3 mmol/L	16.475 ± 5.7876	17.367 ± 4.3844	0.714
ABG- PO mmHg	102.9 ± 36.885	116.7 ± 69.36	0.288
ABG-PCO2 mmHg	26.9 ± 6.658	24.37 ± 2.47	0.464
Cholesterol (mg/dl)	119 ± 38.245	116 ± 22.48	0.278
Triglyceride (mg/dl)	91.5 ± 41.929	139 ± 81.413	0.109
ALT (U/l)	22.91 ± 11.256	26.36 ± 8.009	0.235
AST (U/l)	33.64 ± 17.113	53.12 ± 10.857	0.773
ALP (U/l)	213.57 ± 109.196	363.8 ± 277.156	0.041
Direct. Bilirubin (mg/dl)	0.177 ± 0.158	0.215 ± 0.087	0.478
Total Bilirubin (mg/dl)	0.441 ± 0.4432	0.372 ± 0.1446	0.238
WBC ($\times 10^3/\mu l$)	9.959 ± 4.3708	8.25 ± 3.4239	0.434

Hb (g/dl)	**9.718 ± 1.764**	**8.525 ± 2.8605**	**0.259**
PLT (×10³/µl)	**375.5 ± 169.956**	**483.5 ± 91.176**	**0.238**

Table 2 compares various parameters comprehensively between two groups: patients with a family history of PA and patients without a family history. The family history signifies the presence of a sibling who has received a definitive diagnosis of PA. The mean values and standard deviations for each parameter were reported, along with the corresponding p-values. The family history signifies the presence of a sibling who has received a definitive diagnosis of PA.

The results indicated that the parameter ammonia exhibited a significant difference between the two groups. The mean level of ammonia among patients with a family history group (107.78 ± 29.89 mg/dl) was significantly higher than that among patients without a family history (82 ± 14.024 mg/dl) ($p = 0.005$).

Another parameter, PH, also showed a statistically significant difference between the two groups. The group with a family history of PA had a lower mean arterial blood pH (7.3119 ± 0.12128) compared to the group without a family history (7.4389 ± 0.06139). This finding suggested a difference in an acid-base balance associated with the presence of a family history of the disease ($p = 0.04$)

In contrast, no significant differences were observed between the two groups for parameters such as total protein, albumin, urea, creatinine, vitamin D, sugar, ABG-PCO3, ABG-PO, and ABG-PCO2.

However, the creatinine levels were a significant difference ($p = 0.047$), with a mean value of 0.425 ± 0.1 mg/dl among the family

history group and 0.45 ± 0.2517 mg/dl among those without a family history group.

Parameters such as sodium, potassium, phosphor, and calcium were not shown statistically significant differences between the two groups.

Table 2 shows the comparison of various parameters between the patients with and without a family history of PA. The results indicated that there were no statistically significant differences in cholesterol levels between the two groups ($p = 0.278$). Similarly, the two groups observed no significant difference in triglyceride levels ($p = 0.109$).

ALT levels also showed no significant difference between patients with a family history of the disease and those without a family history ($p = 0.235$). Similarly, the two groups observed no significant difference in AST levels ($p = 0.773$).

Regarding ALP, patients with a family history of PA had a mean value of 213.57 ± 109.196 mg/dl, while those without a family history had a mean value of 363.8 ± 277.156 mg/dl. That indicates the statistically significant ($p = 0.041$). Meanwhile, there were no significant differences found in direct bilirubin (family history of PA: 0.177 ± 0.158 mg/dl, no family history: (0.215 ± 0.087 mg/dl) ($p = 0.478$) and total bilirubin (family history of the disease: 0.441 ± 0.4432 mg/dl, without family history: 0.372 ± 0.1446) ($p = 0.238$).

Additionally, there were no statistically significant differences in WBC ($p = 0.434$), Hb ($p = 0.259$), and PLTs ($p = 0.238$).

Table 3: Distribution of PA cases from 2011 to 2022

Consanguineous Couples	Frequency	Percent
Yes	16	64 %
No	9	36 %
Total	25	100 %

Table 3 shows the distribution of cases from 2011 to 2020. The majority of cases were diagnosed between the years 2014 and 2016 with 36%. Followed by 28% of cases diagnosed between 2017 to 2019. 16% of total cases were reported between 2020 and 2022.

Table 4: The Distribution of Study Cases According to Consanguineous Couples

Year of diagnosis	Number of cases	Percent
2011 – 2013	5	20 %
2014 – 2016	9	36 %
2017 – 2019	7	28 %
2020 – 2022	4	16 %
Total	25	100 %

Table 4 shows the distribution of cases included in the study based on consanguineous couples or non-consanguineous couples. The data presented in this table, derived from the study population of 25 cases, showed that 16 cases (64%) were from consanguineous couples, while the remaining nine cases (36%) were non-consanguineous couples.

The high percentage of cases born to consanguineous couples in this study suggested a possible association between consanguinity and the development of PA.

4. DISCUSSION:

Propionic acidemia (PA) is an autosomal-recessive inborn error of metabolism resulting from a deficiency in PCC. It disrupts the metabolism of branched-chain amino acids and exhibits variable prevalence across different populations and geographic

regions. The aim of the present study was to investigate the impact of sex and family history on biochemical and hematological parameters among PA patients .

As shown in table 1 focused on the influence of sex on the parameters. The findings indicated that there is no significant effect of sex on the levels of ammonia, total protein, albumin, urea, creatinine, sodium, potassium, phosphorus, calcium, vitamin D, sugar, and arterial blood gas parameters (pH, PCO3, PO2, PCO2) among patients with PA .

Table 2 focused on the impact of family history on the measured parameters. Revealed that patients with a family history of PA exhibited significantly higher ammonia levels than those without a family history. A characteristic of PA, especially valuable as a pointer to an inborn error of metabolism, is hyperammonaemia, found in 88% of all patients. In addition, hematological abnormalities were frequently observed [19]. This notable difference suggests a plausible association between the presence of a family history of the disease and elevated ammonia levels. Furthermore, a statistically significant discrepancy in arterial blood pH between the two groups was observed, indicating a potential disparity in an acid-base balance associated with the presence of family history. In 90% of all patients severe metabolic acidosis was present [20]. However, no statistically significant differences were found in other parameters, including total protein, albumin, urea, creatinine, vitamin D, sugar, and arterial blood gas parameters (PCO3, PO2, PCO2). This table provides additional insights into the impact of family history on parameters such as cholesterol, triglyceride, ALT, AST, ALP, bilirubin (direct and total), WBC, Hb, and PLT counts. The results from this study

indicate that the presence or absence of a family history of PA did not have a statistically significant influence on these parameters within the studied population.

The distribution of cases based on the diagnosis dates indicates that most cases were diagnosed between 2014 and 2016, followed by cases between 2017 and 2019. A relatively low number of cases were diagnosed between the years 2020 and 2022.

The demographic information about the study population, specifically the distribution of PA among consanguineous couples. The study reveals a high percentage of cases born to consanguineous couples. Our findings are in agreement with previous study that shows consanguinity was reported in 47% of parents in Turkey. In Turkish families, the consanguinity rate was 95%, with most parents being second-grade relatives [21].

5. CONCLUSION:

This research highlights the effect of gender, family history, and consanguineous couples on some biochemical and hematological parameters among PA patients. Although sex was not significant impact on the measured parameters, the family history was associated with elevated ammonia levels and acid-base balance. The present study suggests that there is relationship between consanguineous marriage and the inherited factors of PA disease. Further research should be conducted to investigate the distribution of consanguineous couples and unaffected newborn children with PA. These findings highlight the necessity for further research to investigate the specific genetic variations and underlying mechanisms contributing to the pathogenesis of PA.

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