**DOI: https://doi.org/10.31351/vol29iss2pp259-262**

# The Frequency Inborn Error of Mitochondrial Function in Mosul and Kurdistan Region

**Muhammad A. Ahmed[*,1] , Mwafak K. Hasan[**] and Ashwaq N. Abbas[***]**

[*]College of Pharmacy, University of Mosul.
[**]College of Science, University of Mosul.
[***]College of Dentistry, University of Sulamiania,

## Abstract

This work aimed to estimate the frequency of mitochondrial inborn errors of metabolism (MIEMs) in patients presenting with family history and IEM-picture who referred for advance IEM assay in Mosul province and Kurdistan region. This study was observational study conducted on 364 cases referred from different general /or private pediatric clinics with unexplained sign and symptoms and suspension of mitochondrial dysfunction. The study included 364 children with an age ranging from 1 month to 1 year. Started from January 2018 to January 2020. All patients referred with their full history review, notes about their clinical examination, and laboratory investigations including blood ammonia, serum lactate/ pyruvate, arterial blood gases. In addition to the standard laboratory-tests (kidney and liver functions, blood glucose, and complete blood picture) carried out in Sorain private Laboratory. The results of this work show that **s**ixteen (4.4%) of cases were positive in the IEM screening test. There were 4 (1%) patients with a definitive mitochondrial related error of metabolism, 2 (0.5%) of the cases due to Carnitine Uptake Defect and 1 (0.2%) Short Chain Acyl CoA Dehydrogenase Deficiency and other one patient (0.2%) case caused by 3-Methylcrotonyl CoA Carboxylase Deficiency. In conclusion, the incidence of mitochondrial inborn errors of metabolism (MIEMs) between patients presenting with IEM was higher in Mosul and Kurdistan region than international values

**Keywords: Mitochondria, An inborn error of metabolism, Carnitine, Mosul.**

# تكرار حالات الخلل الوراثي في وظائف المايتوكوندريا في الموصل وافليم كردستان العراق

**محمد عبد الغفور احمد القطان*[،1] ، موفق خليل حسن ** و اشواق نجم الدين عباس *****

* كلية الصيدلة ، جامعة الموصل .
** كلية العلوم ، جامعة الموصل .
*** كلية طب الاسنان ، جامعة السليمانية .

## الخلاصة

يهدف هذا العمل لتقدير تكرارألاخطاء في تمثيل الغذائي الوراثية في بيوت الطاقة عند المرضى الذين لديهم تاريخ عائلي و اعراض خلل في بيوت الطاقة وألذين ارسلوا لفحص تكرارألاخطاء في تمثيل الغذائي المتقدم في محافظة الموصل وإقليم كردستان. أجريت هذه الدراسة على ٣٦٤ مريضًا تمت إحالتهم من عيادات أطفال عامة أو خاصة مختلفة مع علامات وأعراض غير مفسرة وتعليق بالخلل في بيوت الطاقة. تضمنت الدراسة ٣٦٤ طفلاً تتراوح أعمارهم بين شهر واحد وسنة واحدة. بدءت الدراسة في كانون الثاني ٢٠١٨ و انتهت في كانون الثاني ٢٠٢٠. تمت إحالة جميع المرضى بمراجعة كاملة لتاريخهم المرضي ، وملاحظات فحصهم السريري ، والفحوصات المخبرية بما في ذلك أمونيا الدم ، حامض اللبنيك / البيروفات في الدم ، غازات الدم الشريانية. بالإضافة إلى التحاليل المختبرية القياسية (وظائف الكلى والكبد ، جلوكوز الدم ، صورة الدم الكاملة) فيمختبر سوران الاهلي. بينت نتائج هذا العمل ان ستة عشر (٤,٤ ٪) من المرضى إيجابيين مصابين باحد أخطاء التمثيل الغذائي الخلقية .كان هناك ٤ (١٪) من المرضى الذين يعانون من خطأ استقلابي متعلق ببيوت الطاقة ، و ٢ (٠,٥٪) من الحالات بسبب عيب امتصاص الكارنيتين و ١ (٠,٢٪) من نقص سلسلة Acyl CoA Dehydrogenase وحالة أخرى (٠,٢٪) الناجم عن نقص ٣ Methylcrotonyl CoA Carboxylase . نستنتج من هذا العمل ان معدل حدوث أخطاء التمثيل الغذائي الخلقية في بيوت الطاقة بين المرضى الذين يعانون من ألاخطاء في تمثيل الغذائي الوراثية في الموصل وإقليم كردستان أعلى من القيم الدولية.

**الكلمات المفتاحية: بيوت الطاقة ، خطأ وراثي في التمثيل الغذائي ، كارنيتين ، الموصل.**

## Introduction

Hundreds of single-gene anomaly are involved in inborn errors of metabolism [(1)]. Inborn errors of metabolism are often rare multisystem disorders with neurological and non-neurological manifestations, commonly with onset during in infancy, childhood, and adulthood and many of them fatal if not treated. Inborn errors of metabolism disorders in lead to abnormal metabolism and this lead to improper metabolism of nutrients and energy production[(2)]. The disorders usually caused by the absence or abnormality of the substrate, enzyme or its cofactor, leading to either accumulation or deficiency of a specific metabolite[(3)]. The mitochondrial error cause significant effects on neonate life by affecting different aspect of mitochondrial activities e.g. fatty acid β-oxidation in mitochondria. These patients present with clinical features may include but not restricted to[(4)] failure to thrive, chronic vomiting, chronic diarrhea, hypoglycemia, disturbed conscious level, seizures,

[1]Corresponding author E-mail**:** ashwaq73@yahoo.com
Received: 22/5 /2020
Accepted: 31/8/2020

delayed motor response , hypotonia or hypertonia, spasticity, mental retardation, muscle weakness, walking abnormalities, microcephaly, speech abnormalities of the patients, Hepatomegaly, cardiac manifestation and ophthalmic manifestation[4].

Mitochondrial inborn error disorders are inherited metabolic diseases caused by either complete or partial deficiency of specific enzymes or transport proteins that involved in the mitochondrial metabolism. The mitochondrial inborn disorders have an incidence of 1 to 100,000 births[5] worldwide. However, in the Middle East population, the incidence may approach 20 to 100,000[6] births with no clear data present from Iraq. The mitochondrial dysfunction screening process has evolved for better understanding of these conditions, availability of diagnostic tools and treatment option development. The inclusion of specific test in newborn screening list has become controversial with varying practices and national need.

**Aim:** This work focuses on explains the exact frequency of the mitochondrial dysfunction between patients with an inborn error of metabolism in Mosul and Kurdistan region.

## Patient and Methods

The study included three hundred and sixty-four newborn and infant with an age ranging from 1 month to 1 year. Patient refers to different general and private hospitals and clinics in Mosul and Kurdistan region to Soran private hospital laboratory started from January 2018 to January 2020 with the symptom of inborn error of metabolism that includes poor feeding, vomiting, diarrhea, and/or dehydration, temperature instability, tachypnea, apnea, seizures, hypotonia, lethargy and coma. In addition to the family history of any inborn error of metabolism and follow primary care, physician (PCP) guidelines for IEM diagnosis [7] (see Table-1). All patients referred to pediatrician with their full history review, notes about their clinical examination, and laboratory investigations including blood ammonia, arterial blood gases. In addition to the standard laboratory tests (kidney and liver functions, blood glucose, and complete blood picture kept for their patients record and not included in this work). All patients who included in this work have at least five above symptom. Brain imaging study conducted for all cases before referral with either CT scan or MRI to rule out any intracranial anomaly, diseases or trauma. The cases with their results referred back to their physician for follow up.

**Table 1. Primary care physician guidelines for IEM diagnosis[7]**

| |
|---|
| It considered when diagnose and treat bacteremia, encephalopathy due to severe hypoxia or toxins ingestion. |
| When laboratory- tests fail to give a definitive diagnosis. |
| Symptoms did not respond even after treatment. |
| Present as acute illness or as chronic |
| Recurrent or progressive condition at any age |
| Negative family history for genetic or metabolic disorder does not exclude. |
| Neonatal death from unknown causes. |

The samples collected over a two-year interval. Blood drop from the heel of the neonate collected before 24hrs of protein feedings the sample adsorbed to the specific type of filter paper then sample packaged in standard transport package as recommended by the manufacturer for NeoLab– Greece for tandem mass spectrometry analysis to detection and quantification of metabolic compounds. In addition to 5 ml of whole blood were collected in plan tube for serum lactate and pyruvate estimation using Cayman fluorescence-based Kits (No. 700510 and No. 700470 respectively)[8,9]. The results return to Soran hospitals then sent it to physicians.

The parents of the subjects involved in this study informed about the purpose of the study and the plan of work before they agreed to participate. Statistical analysis conducted using manual methods to calculate the percentage of the obtained data of the patients.

## Results

In this study, there were 364 patients referred with unexplained symptoms with the suspension of mitochondrial inborn error of metabolism. Patients referred to different general and private pediatric hospitals and clinics, with their ages ranging from 1 day to 12 months.

Infants of age <1 month numbered 266 (73%) and newborn aged from 2-12 months numbered 98 (27%); the number of females was 247(68%) and males represent 116 (32%). Patients with positive IEM consanguinity numbered 236 (65%), and 73 (20%) patients had a strong positive family history and 55 (15%) patients with no mitochondrial or other IEM history. Only 16 (4.4%) patient of patients were confirmed diagnosed with one of IEM with only 4 (1%) cases approved to have a mitochondrial related inborn error of metabolism 2 (0.5%) of the cases due to Carnitine Uptake Defect and 1 (0.2%) Short Chain Acyl CoA Dehydrogenase Deficiency (SCADD) and other 1 (0.2%) case caused by 3-Methylcrotonyl CoA Carboxylase Deficiency (3-MCCD) as in Table 2. In addition to tandem mass spectrometry analysis serum lactate/ pyruvate ratio shows significant elevation over 20 in

only 25 (6.8%) of the cases. Mitochondrial related inborn error of metabolism patient shows significant elevation over the normal range of serum lactate was 1615.2± 208.6 µmol/L in comparison with the normal newborn 1250±110 µmol/L, serum pyruvate 70.62±7 µmol/L compared to 63±0.2 and lactate to pyruvate ratio 22.8±1.24 which reflect severe mitochondrial dysfunction.

**Table 2. Mitochondrial inborn error of metabolism cases**

| No. | **The metabolic error of diseases** | **Patient value** | **Reference value** | **Case No.** | **Frequency** |
|---|---|---|---|---|---|
| 1. | Short Chain Acyl CoA Dehydrogenase Deficiency (SCADD) | C4=2.06,<br>C4/C3=2.19<br>C4/C2=0.15<br>C4/C8=22.89 | C4 < 1.02<br>C4/C3 < 0.65<br>C4/C2 < 0.05<br>C4/C8 < 22 | 1 | 0.2% |
| 2. | Carnitine Uptake Defect | C0=5.60<br>C0=6.32 | C0 > 10.4 | 2 | 0.5% |
| 3. | 3-Methylcrotonyl CoA Carboxylase Deficiency (3-MCCD) | C5OH=2.99,<br>C5OH/C8=16.61<br>C5OH/C0=0.26 | C5OH < 0.41<br>C5OH/C0 < 0.026<br>C5OH/C8 < 12.5 | 1 | 0.2% |

**C0 = free carnitine, C2-actyle C3 = propionyl, C4 = butyryl, C5OH = 3-hydroxy, isovaleril, C6 = hexanoyl, C8 = octanoyl.**

## Discussion

Mitochondrial inborn error of metabolism is a part of newborn screening for IEM in that approved by WHO. Anomalies of mitochondrial function are characteristics of these metabolic disorders[10]. The mitochondria play a vital role in the regulation of many cellular homeostatic mechanisms; through the production of ATP, reactive spices (both ROS and RNS), autophagy, apoptosis and biogenesis[11]. The signaling pathways such as sirtuins (SIRT1-7) and peroxisome-proliferator-activated receptor γ co-activator-1α (PGC-1α) and antioxidant mechanisms as Mn-dependent superoxide dismutase (MnSOD) should check carefully as it is not correct to describe the relationship between phenotype and genotype in these patients as straightforward relation[11].

Inborn error of mitochondrial metabolism patients presented with seizures with or without hypoglycemia, metabolic acidosis with the fall of sucking and coma. Fatty liver associated with prolonged keto-genic stresses usually after 7 days of fibril condition hepatomegaly needs longer time (weeks) to be developed[12]. Based on the published data, the incidence of both SCADD and 3-MCCD worldwide not exceeding 1 in 50,000 (0.002%) [13] while our result shows that the frequency in our sample was 0.2% which is higher than international values. Similarly, the incidence of carnitine deficiency is approximately 1 in 100,000 newborns worldwide[14,15].

The elevated lactate/pyruvate ratio suggesting inborn errors of ketogenesis as described. The significant elevation of plasma butyryl-carnitine with or without elevation ethyl-malonic acid (C4) concentrations with a reduction in plasma free carnitine (C0) considered as a biochemical signature of inborn error of mitochondria [16] which was seen in one of the cases in this work who presented with hypotonia, seizures, metabolic acidosis after flu with hypoglycemia.

## Conclusion

To sum up, the Frequency of mitochondrial IEM (MIEMs) between patients presenting with IEM was higher in Mosul and Kurdistan region than international values.

## References

1. Arnold GL. Inborn errors of metabolism in the 21st century: past to present. Ann Transl Med. 2018;6(24):467-467.
2. Ebrahimi-Fakhari D, Van Karnebeek C, Münchau A. Movement Disorders in Treatable Inborn Errors of Metabolism. Mov Disord. 2019;34(5):598-613.
3. Inborn errors of metabolism: Classification - UpToDate. https://www.uptodate.com/contents/inborn-errors-of-metabolism-classification. Accessed July 31, 2020.
4. Wajner M, Amaral AU. Mitochondrial dysfunction in fatty acid oxidation disorders: Insights from human and animal studies. Biosci Rep. 2016;36(1):281.
5. Khan NA, Govindaraj P, Meena AK, Thangaraj K. Mitochondrial disorders: Challenges in diagnosis & treatment. Indian J Med Res Suppl. 2015;141(JAN 2015):13-26.
6. Gorman GS, Schaefer AM, Ng Y, et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. Ann Neurol. 2015;77(5):753-759.
7. Agana M, Frueh J, Kamboj M, Patel DR, Kanungo S. Common metabolic disorder (inborn errors of metabolism) concerns in primary care practice. Ann Transl Med. 2018;6(24):469-469.

8. L-Lactate Assay Kit | Cayman Chemical. https://www.caymanchem.com/product/700510. Accessed July 29, 2020.
9. Pyruvate Assay Kit (Pyruvic Acid Assay Kit) | Cayman Chemical. https: //www .caymanchem .com/product/700470/pyruvate-assay-kit. Accessed July 29, 2020.
10. Van Rijt WJ, Koolhaas GD, Bekhof J, et al. Inborn Errors of Metabolism That Cause Sudden Infant Death: A Systematic Review with Implications for Population Neonatal Screening Programmes.Neonatology. 2016 ; 109 (4) :297-302.
11. Ahmed M. Exploring the impact of hypoxia mimetic agents on multipotent stem cell biology. Keele Univ. 2018.
12. Rice GM, Steiner RD. Inborn errors of metabolism (metabolic disorders). Pediatr Rev. 2016;37(1):3-17.
13. Lisyová J, Chandoga J, Jungová P, et al. An unusually high frequency of SCAD deficiency caused by two pathogenic variants in the ACADS gene and its relationship to the ethnic structure in Slovakia. BMC Med Genet. 2018;19(1).
14. Stanley CA. Carnitine deficiency disorders in children. In: Annals of the New York Academy of Sciences. Vol 1033. New York Academy of Sciences; 2004:42-51.
15. Lam C, Carter JM, Cederbaum SD, et al. Analysis of cases of 3-methylcrotonyl CoA carboxylase deficiency (3-MCCD) in the California newborn screening program reported in the state database. Mol Genet Metab. 2013;110(4):477-483.
16. Short-Chain Acyl-CoA Dehydrogenase Deficiency - GeneReviews® - NCBI Bookshelf. https: //www .ncbi. nlm.nih .gov/ books/ NBK63582/. Accessed July 31, 2020.