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Incidence of Hyperammonemia among High-Risk Infants Admitted to Pediatric Intensive Care Unit

Mohamed Mamdouh Gaafar, Ali Ahmed Mohammed*, Wesam A. Mokhtar
Pediatrics Department, Faculty of Medicine, Zagazig University, Egypt
***Corresponding author**: Ali Ahmed Mohammed, **Mobile:** (+20)01235867601, **Email:** aaliali198619861986@gmail.com

ABSTRACT

Introduction: Severe liver failure and inborn metabolic abnormalities produce hyperammonemia in children. Because of the pre-analytical challenges that must be properly controlled, achieving valid plasma ammonia levels in acute instances might be difficult.

Objective: The aim of the present study was to estimate the prevalence of plasma ammonia levels among high risk infants admitted to pediatric intensive care unit (PICU).

Patients and Methods: A cross-sectional study was carried out at NICU in Pediatric Department at Zagazig University Children Hospital. This study involved 60 neonates and children who were subjected to full medical history, thorough clinical examination and laboratory investigations. Frequency of suspected and confirmed inborn errors of metabolism (IEMs) cases was assessed.

Results: The mean age was 2.15±1.89 years and weight was 8.95±6.56, 50.0% were male, regarding mode of delivery in 66.7% was cesarean section (CS). 48.3% had consanguinity. The main complaints for patients were respiratory distress (51.7%), convulsion (33.3%) and encephalopathy (10%) and the hyperammonemia was detected in 25% of the studied group. The hyperammonemia was detected in 66.7% of the confirmed IEM cases. About 16 cases (26.7%) of the studied group, unfortunately, died while 73.3% survived.

Conclusion: Hyperammonemia represented a one of the main significant cause of sick infants' admission to PICU. Hyperammonemia must be rapidly suspected in case of neurologic symptoms in pediatrics. An adequate management should start rapidly as coma duration and ammonia peak level.

Keywords: Hyperammonemia, Inborn Errors of Metabolism, Pediatric Intensive Care Unit.

INTRODUCTION

Inborn errors of metabolism (IEMs) are a phenotypically and genetically diverse group of metabolic illnesses caused by malfunctioning enzymes, cofactors, and transporters, which result in the accumulation of toxic substrates, the production of by-products, and reduced product levels, resulting in a variety of clinical manifestations [(1)]. Clinical indicators include acute metabolic crisis, convulsions, metabolic acidosis, severe low blood sugar, high blood ammonia, and diverse organ damage. Some of these are treatable, but if not treated in a timely manner, they can result in irreparable physical disability, mental retardation, and even death [(2)].

Hyperammonemia is a life-threatening condition that can result in brain damage and edema[(3)]. A plasmatic level more than 80 mol/L in babies under one month of age and greater than 55 mol/L in older children is considered hyperammonemia [(4)].

Ammonia is produced when proteins are broken down during amino acid metabolism, and 90% of it enters the urea cycle and is transformed to urea. The glutamine synthase enzyme is found in the brain, kidneys, and skeletal muscle and is responsible for the elimination of ammonia, which is either excreted in urine or utilised by the stomach for energy synthesis. Ammonia accumulates and is shunted to the systemic circulation when removal is inhibited or production is increased, resulting in brain buildup and eventual dysfunction [(2)].

Hyperammonemia is treated by 1) identifying precipitating events and the existence of cerebral edema, 2) lowering ammonia production by reducing protein intake and reversing catabolism, and 3) removing ammonia with pharmacologic treatment and, in the most severe instances, extracorporeal therapies. In situations of severe coma, transcranial Doppler ultrasonography can be used to noninvasively monitor cerebral blood flow and titrate treatment[(5)].

This study aimed to early detection of plasma ammonia level among high risk infants admitted to pediatric intensive care unit (PICU), Zagazig University Children Hospital in order to provide early treatment of treatable and transient disorders associated with IEM (Inborn Errors of Metabolism).

PATIENTS AND METHODS

This cross-sectional prospective study was conducted during the period from December 2019 to January 2020. It included 60 cases admitted to Pediatric Intensive Care Unit (PICU) aged from 28 days to 14 years. This study was conducted at Pediatric Department, Faculty of Medicine, at Zagazig University.

Inclusion criteria:

Children from 28 days to 14 years of age, of both gender. Lethargy, poor feeding, frequent vomiting, intractable seizures, rapid deep breathing, and unexplained neurological indications in a previously healthy infant were all hallmarks of IEM. Unusual developmental delays, repeated unexplained encephalopathy, skin and hair changes, or ocular abnormalities in children.

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Exclusion criteria:

Patient outside age (below 28 days or above 14 years). These with brain trauma, toxicology, tumors and chromosome anomalies, and parents refuse to share in the study.

Ethical Consideration:

The study was approved by the Local Ethical Committee of Zagazig University. Written consent was obtained from the parent of every patient prior to the procedures. This study has been carried out in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

All studied cases were subjected to:

1. **Full history taking** with special stress on age, residence, mode of delivery, developmental history, nutritional history, family history including consanguineous marriage, previous similar condition in the family, genetic or metabolic diseases in the family, previous sibling death and history of previous abortion.
2. **Full clinical examination**: General examination (Anthropometric measurement, vital signs, general appearance and general condition). Skeletal examination including any skeletal deformity Cardiac examination including evidence of congenital heart disease or cardiomyopathy. Abdominal examination for organomegaly. Neurological examination including evidence of hypotonia, convulsion or encephalopathy. Chest examination and abnormal body odor.
3. **Routine laboratory investigation:** All children were subjected to routine laboratory investigation according to local PICU protocol according to cause of admission.

Plasma ammonia measurement: were measured by colorimetric method (Cobas Integra Auto analyzer, Germany) [(4)]. Values of 50-80 μg/dl were considered normal ranges of plasma ammonia and the values above 150 μg/dl were considered hyperammonemia. Plasma ammonia was measured in biochemistry central lab, Biochemistry and Microbiology Department, Zagazig University. The hyperammonemia was considered when ammonia was more than 100 mg/dl in critical infant.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for the Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Qualitative data were represented as frequencies and relative percentages. Quantitative data were expressed as mean ± SD (Standard deviation), median, and range.

RESULTS

The demographic data of the studied group are shown in table 1.

Table (1): Demographic data of the studied group

Variable	(n = 60)		
Age (years)	**Mean± SD**	**2.15±1.89**	
	Median (Range)	**1.0 (0.1-11)**	
Weight (kg)	**Mean± SD**	**8.95±6.56**	
	Median (Range)	**7.0 (2.5-35.0)**	
		N	**%**
Sex	**Male**	**30**	**50.0**
	Female	**30**	**50.0**
Mode of delivery	**CS**	**40**	**66.7**
	NVD	**20**	**33.3**
Consanguinity	**-VE**	**31**	**51.7**
	+VE	**29**	**48.3**
Previous sibling deaths	**-VE**	**51**	**85.0**
	+VE	**9**	**15.0**
Previous hospitalization	**-VE**	**38**	**63.3**
	+VE	**22**	**36.7**
Previous abortion	**-VE**	**47**	**78.3**
	+VE	**13**	**21.7**
Genetic or metabolic disease in family	**-VE**	**60**	**100.0**
	+VE	**0**	**0.0**
	Total	**60**	**100.0**

The main complaint for patients was respiratory distress in 51.7% of the patients **(Table 2)**.

Table (2): Initial clinical presentation among studied group

Initial clinical presentation		N = 60	%
Vomiting	**-VE**	**37**	**61.7**
	+VE	**23**	**38.3**
Diarrhea	**-VE**	**49**	**81.7**
	+VE	**11**	**18.3**
Dehydration	**-VE**	**39**	**65.0**
	+VE	**21**	**35.0**
Convulsion	**-VE**	**40**	**66.7**
	+VE	**20**	**33.3**
Hypotonia	**-VE**	**53**	**88.3**
	+VE	**7**	**11.7**
Respiratory distress	**-VE**	**29**	**48.3**
	+VE	**31**	**51.7**
Apnea	**-VE**	**55**	**91.7**
	+VE	**5**	**8.3**
Encephalopathy	**-VE**	**54**	**90.0**
	+VE	**6**	**10.0**
Jaundice	**-VE**	**59**	**98.3**
	+VE	**1**	**1.7**
Pallor	**-VE**	**50**	**83.3**
	+VE	**10**	**16.7**
Developmental delay	**-VE**	**56**	**93.3**
	+ VE	**4**	**6.7**
Skin manifestation	**-VE**	**58**	**96.7**
	+VE	**2**	**3.3**
Bleeding tendency	**-VE**	**58**	**96.7**
	+VE	**2**	**3.3**
Liver failure	**-VE**	**58**	**96.7**
	+VE	**2**	**3.3**
Cardiac failure	**-VE**	**55**	**91.7**
	+VE	**5**	**8.3**
	Total	**60**	**100.0**

Initial laboratory investigation was performed upon admission. Table 3 shows that 85% had initial positive CRP results among the studied group. The mean plasma ammonia level among the studied group was 117.87.

Table (3): Distribution of laboratory parameters among studied group

Variable	(n = 60)		
HB (gm/dl)	**Mean± SD**	**11.25±2.57**	
WBCs $\times 10^3$	**Mean± SD**	**14.37±3.21**	
PLT $\times 10^3$	**Mean± SD**	**232.71±15.9**	
ALT (U/dl)	**Mean± SD**	**54.6±4.88**	
AST (U/dl)	**Mean± SD**	**84.6±4.55**	
BUN (mg/dl)	**Mean± SD**	**16.952.36**	
Cr (mg/dl)	**Mean± SD**	**0.56±0.04**	
PT (sec)	**Mean± SD**	**12.95±2.74**	
PTT(sec)	**Mean± SD**	**34.29±5.62**	
INR	**Mean± SD**	**1.0±0.2**	
Glucose (mg/dl)	**Mean± SD**	**80.19 ± 8.8**	
Ammonia (mg/dl)	**Mean± SD**	**117.87±8.73**	
Lactate (mg/dl)	**Mean± SD**	**7.53±1.87**	
Na+ (mEq/dl)	**Mean± SD**	**137.8±6.52**	
K+(mEq/dl)	**Mean± SD**	**4.32±1.16**	
Ca++ (mg/dl)	**Mean± SD**	**8.08±1.48**	
Cl^- (mEq/dl)	**Mean± SD**	**6.04±1.46**	
Mg^{++} (mEq/dl)	**Mean± SD**	**2.23±0.23**	
CRP (mg/dl)	**-VE**	**9**	**15**
	+VE	**51**	**85**
PCT (ng/ml)	**-VE**	**56**	**93.3**
	+VE	**4**	**6.7**

HB: hemoglobin; **WBCs**: white-blood-cells; **PLT**: platelets; **ALT**: alanine-aminotransferase; **AST**: aspartate-aminotransferase; **BUN**: blood urea nitrogen; **Cr**: creatinine; **PTT**: partial thromboplastin time; **PT**: prothrombin time; **INR**: international normalized ratio; **Na**: sodium; **K**: potassium; **Ca**: calcium; **Cl**: chloride; **Mg**: magnesium; **CRP**: C-reactive protein; **PCT**: procalcitonin.

The hyperammonemia was detected in 25% of the studied group **(Table 4)**.

Table (4): Frequency distribution of hyperammonemia among studied group

Variable		N	%
Hyperammonemia*	**-VE**	45	75
	+VE	15	25
	Total	60	100.0

16 cases (26.7%) of the studied group died **(Table 5)**.

Table (5): Outcome among studied group

Variable		N = 60	%
Outcome	**Died**	**16**	**26.7**
	Survived	**44**	**73.3%**
	Total	**60**	**100.0**

5% of studied groups were confirmed to have an underlying inborn error of metabolism **(Table 6)**.

Table (6): Frequency distribution of suspected and confirmed* IEM cases among studied group

Variable		N = 60	%
Suspected IEM Cases	**No**	**40**	**66.7%**
	Yes	**20**	**33.3%**
	Total	**60**	**100.0**
Confirmed IEM Cases	**No**	**57**	**95%**
	Yes	**3**	**5%**
	Total	**60**	**100.0**

***Confirmed Cases: confirmed by EMS and a specific confirmatory test.**

The hyperammonemia was detected in 66.7% of the confirmed IEM cases **(Table 7)**.

Table (7): Frequency of hyperammonemia among confirmed* IEM cases (n=3)

Variable		N	%
Hyperammonemia	**-VE**	1	33.3
	+VE	2	66.7
	Total	3	100.0

DISCUSSION

Acute hyperammonemia can lead to neurologic issues, which can quickly progress into a life-threatening situation. Coma length, ammonia peak level, and hyperammonemia duration are the main risk factors for hyperammonemia-related neurologic deficits and mortality [5,6]. The current study aimed to investigate hyperammonemia levels among high risk infants admitted to PICU.

In the present study, the mean age was 2.15±1.89 years and weight was 8.95±6.56, 50.0% were males and 50.0% were females, regarding mode of delivery 66.7% delivered by CS and 33.3% were by NVD. This came to some extent in agreement with **Khalaf *et al.*** [7] who found that 61% of the studied cases were males and 39% were females.

In the present study, 48.3% had consanguinity and 15.0% of studied group had history of previous sibling death, 36.7 % had history of previous hospitalization, 36.7% had history of previous abortion and no one had previous history of genetic or metabolic disease among family. This came in agreement with a study done by **Shawky *et al.*** [8] in which 17 patients (43.5%) had consanguineous parents. Also, **Khalaf *et al.*** [7] found that 61% of patients had consanguinity.

In the current study, the main complaints for patients were respiratory distress (51.7%), vomiting (38.3%) followed by dehydration (35%), convulsion (33.3%), diarrhea (18.3%), pallor (16.7%) and hypotonia (11.7%). The skin manifestation was found in two cases (3.3%), bleeding tendency in two cases (3.3%), and liver failure presented in two cases also (3.3%). Moreover, cardiac failure was presented in 5 cases (8.3%).

Our findings were slightly in agreement with the study of **Selim *et al.*** [9] who found that common presenting features encountered in Egyptian patients were developmental delay 75.9%, Vomiting dehydration 42.9%, and hypotonia 22.2%. Also, **Lund *et al.*** [10] reported that the predominant symptoms in neonates suggesting the possibility of metabolic disorders were convulsions and lethargy.

Savy *et al.* [5] reported that the initial workup of hyperammonemia is guided by a clinical examination and can include the following laboratory investigations: blood gas, electrolytes and anion gap measurement, ketonuria, glycemia, lactic acid, liver enzymes and function test (aspartate transaminase, alanine transaminase, bilirubin, gamma-glutamyl transferase, factor V, prothrombin ratio, international normalized ratio), renal function tests (blood urea nitrogen and creatinine).

In the present study, the mean Hb was 11.25±2.57, WBCs, PLT, ALT and AST were 14.37±6.21, 232.71±115.9, 54.6±34.88 and 84.6±41.55 respectively, also BUN and creatinine were (16.95±12.36 and 0.56±0.41 respectively), +ve CRP in 85% and PCT 6.7%. Our findings are in agreement to the results of the recent study of **Besher *et al.*** [11], which demonstrated that the laboratory investigation among study group showed normal Hg, platelet (PLT) and leukocytosis in CBC, and increasing liver enzymes (AST).

The present study shows that the mean random blood glucose among studied group was (80.19 ± 28.8). This finding was confirmed with the study of **Abdel Maksoud *et al.*** [12]**.** In the present study, as regard plasma ammonia and plasma lactate levels, we found that mean plasma ammonia level among the studied group was (117.87 ± 87.73) and ranged from 70 to 900; also the plasma lactate level mean was (7.53±6.87). Our findings were in agreement with **Ames *et al.***[13] who found that peak plasma ammonia levels varied greatly from 164 to 3869 µmol/L with a median peak ammonia of 1035 µmol/L. Median plasma ammonia levels at admission was 680 µmol/L. The present study shows that the hyperammonemia is considered when ammonia is more than 100 mg/dl in critical infant. It is detected in 25% of the studied group. This finding was confirmed with the study of **El-Desouky *et al.*** [14].

Ozanne *et al.* [1] reported that multiples diseases can lead to acute hyperammonemia in children admitted in pediatric intensive care: liver failure (64% of cases), urea cycle disorders (UCDs) (23%), and others (13%) such as exposure to toxics and medications.

Khalessi *et al.* [15] explained perinatal asphyxia as a cause of hyperammonemia, because of the hypoxic stress, which can induce an increasing catabolism with a decrease in hepatic urea synthesis, leading to mild hyperammonemia. In their results among 100 patients with perinatal asphyxia, 20% patients had hyperammonemia above 90 µmol/L, with a mean plasma level of 117±41 µmol/L in asphyxia stages 2 and 3.

Additionally, the present study revealed that, hyperlactatemia was detected 41.7% of the studied group. However, the study of **El-Desouky *et al.*** [14] found hyperlactatemia was detected in 67.2% of the studied group.

The present study shows that the IEM criteria of suspicion: data from history taking, clinical manifestation, and laboratory manifestation. There was 33.3% of the studied groups were suspected to

had an underlying IEM. These finding is confirmed with **Alfadhel and Babiker [16].**

Abdel Maksoud *et al.* [12] estimated the prevalence of inborn errors of metabolism (IEMs) in patients with acute encephalopathy-like symptoms who presented to an emergency room aged 1 to 5 years (ED). The researchers conducted a prospective observational study on 30 kids who were brought to the Pediatric Emergency Department with unexplained acute encephalopathy. All of them were tested for IEMs.

Auron *et al.* [3] reported that transient hyperammonemia of the newborn is a condition of potentially severe hyperammonemia due to transient platelet activation and portosystemic shunting through a large ductus venosus. These children' neurologic results can range from normal development to severe mental impairment and convulsions.

Broomfield and Grunewald [17] revealed that survival with favorable neurologic outcome can be achieved with suitable treatment. Drug-related causes of hyperammonemia are as follows: valproic acid that interferes with glutamine synthesis, carbamazepine, salicylates (Reye's syndrome), topiramate, tranexamic acid, and chemotherapy **[18].**

Therefore, the therapeutic measures to treat hyperammonemia are specifically targeted to decrease ammonia plasma level and to protect the brain from hyperammonemia. To reduce the risk of irreparable brain injury, early detection and treatment are critical [5]. Suspected patients should be transferred as soon as possible to a pediatric ICU, where first-line drugs and consensus-based written guidelines should be available 24 hours a day, seven days a week.

CONCLUSION

We concluded that hyperammonemia represented a one of the main significant cause of sick infants' admission to PICU. Hyperammonemia must be rapidly suspected in case of neurologic symptoms in pediatrics. An adequate management should start rapidly as coma duration and ammonia peak level are both the main risk factors of death.

It should be considered as a differential diagnosis for any sick infants presented with acute emergency manifestation with attentions to consanguinity which is a common tradition in our country.

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Author contribution: Authors contributed equally in the study.

REFERENCES

1. **Deng K, Zhu J, Yu E *et al.* (2021):** Incidence of inborn errors of metabolism detected by tandem mass spectrometry in China: a census of over seven million newborns between 2016 and 2017. Journal of Medical Screening, 28(3): 223-229.
2. **Auger N, Bilodeau-Bertrand M, Brousseau É *et al.* (2022):** Observational study of birth outcomes in children with inborn errors of metabolism. Pediatric Research, 22: 1-7.
3. **Ozanne B, Nelson J, Cousineau J (2012):** Threshold for toxicity from hyperammonemia in critically ill children. J Hepatol., 56(1):123–128.
4. **Auron A, Brophy P (2012):** Hyperammonemia in review: pathophysiology, diagnosis, and treatment. Pediatr Nephrol., 27(2):207–222.
5. **Paprocka J, Jamroz E (2012):** Hyperammonemia in children: on the crossroad of different disorders. Neurologist., 18(5):261–265.
6. **Savy N, Brossier D, Brunel-Guitton C *et al.* (2018):** Acute pediatric hyperammonemia: current diagnosis and management strategies. Hepatic Medicine: Evidence and Research, 10: 105-109.
7. **Khalaf S, El-Tellawy M, Refat N *et al.* (2019):** Detection of some metabolic disorders in suspected neonates admitted at Assiut University Children Hospital. Egyptian J Med Human Gene, 20(1): 1-7.
8. **Shawky R, Abd-El Khalek H, Elakhdar S (2015):** Selective screening in neonates suspected to have inborn errors of metabolism. Egyptian J Med Human Gene, 16(2):165–171.
9. **Selim L, Hassan S, Salem F (2014):** Selective screening for inborn errors of metabolism by tandem mass spectrometry in Egyptian children: a 5 year report. Clin Biochem., 47(9):823–828.
10. **Lund A, Christensen E, Skovby F (2002):** Diagnosis and acute treatment of inborn metabolic diseases in infants. Ugeskrift for Laeger., 164(48):5613–5619.
11. **Besher K, Nieto-Hipolito J, Buenrostro-Mariscal R *et al.* (2021):** Spectrum based power management for congested IoT networks. Sensors (Basel), 21(8):2681-86.
12. **Abdel Maksoud M, Elsayed S, Shatla R *et al.* (2018):** Frequency of inborn errors of metabolism screening for children with unexplained acute encephalopathy at an emergency department. Neuropsychiatr Dis and Treat, 14: 1715–1720.
13. **Ames E, Luckritz K, Ahmad A (2020):** A retrospective review of outcomes in the treatment of hyperammonemia with renal replacement therapy due to inborn errors of metabolism. Pediatr Nephrol., 35(9), 1761-1769.
14. **El-Desouky A, El-Gebally S, Beyoumi T (2020):** Frequency of inborn errors of metabolism among infants with non-apparent causes of failure to thrive in Zagazig University Hospitals. Egyptian J Hosp Med., 81(5), 1948-1952.
15. **Khalessi N, Khosravi N, Mirjafari M *et al.* (2016):** Plasma ammonia levels in newborns with asphyxia. Iran J Child Neurol., 10(1):42–46.
16. **Alfadhel M, Babiker A (2018):** Inborn errors of metabolism associated with hyperglycaemic ketoacidosis and diabetes mellitus: narrative review. Sudanese J Paediatr., 18(1): 10–23.
17. **Broomfield A, Grunewald S (2012):** How to use serum ammonia. Arch Dis Child Educ Pract Ed., 97(2):72–77.
18. **Dubinski I, Feuchtinger T, Maier E *et al.* (2021):** Transient hyperammonemic encephalopathy in a child with relapsed acute lymphoblastic leukemia and severe tumor lysis syndrome. Journal of Child Science, 11(01): 208-211.