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Original Article

Evaluation of the Reasons for Requesting Ammonia Tests in the Pediatric Clinic Over the Last Five Years

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ABSTRACT

Objective: Ammonia is a neurotoxic substance that is produced as a consequence of protein metabolism. It is converted to urea in the liver and subsequently eliminated by the kidneys. Hyperammonemia is defined as values that exceed 60 µmol/L outside of the neonatal period. Hyperammonemia in children is frequently caused by genetic and metabolic conditions, drug use, and liver disease or drug use in adults.

Methods: The results of patients treated at our hospital in the past five years and whose blood levels exceeded 60 µmol/L were evaluated in our single-center retrospective study. The age, gender, ammonia levels, and reasons for obtaining ammonia of the patients were analyzed.

Results: The purpose of the study was to investigate the reasoning behind the request for ammonia testing in pediatric patients at the hospital. The results showed that the reasons for requesting testing varied between children under and over 1 month of age. Although metabolic disorders are usually evaluated in newborns, infections, liver dysfunction, and drug side effects are predominant in children over the age of one month. The retrospective design and single-center aspect of the study have been noted as major limitations.

Conclusion: Hyperammonemia may be an adverse effect of neurological diseases in pediatric patients, and medications used to treat seizures can cause hyperammonemia. This should be kept in mind in patients presenting with seizures, especially those with changes in consciousness.

INTRODUCTION

Ammonia is a toxic chemical produced during the metabolic processing of proteins in the human body. Ammonia, a compound that is naturally produced in the body, is converted into urea, a less harmful product, in the liver via the urea cycle (ornithine cycle) and is eliminated from the body through the kidneys. The breakdown of ammonia is critically important, particularly for the protection of the central nervous system. Elevated ammonia levels are referred to as hyperammonemia. In accordance with the accepted clinical categorization, blood ammonia concentrations above 150 µmol/L in neonates and exceeding 60 µmol/L in adults are referred to as hyperammonemia.[1]

Hyperammonemia is related to several metabolic and genetic disorders characterized by increased ammonia levels in the bloodstream. Hyperammonemia in neonates has been linked to genetic metabolic problems, such as urea cycle disorders (e.g., ornithine transcarbamylase deficiency), organic acidemias (e.g., propionic acidemia and methylmalonic acidemia), and mitochondrial disorders. Urea cycle disorders are characterized by a lack of one or more enzymes involved in the conversion of ammonia to urea, which could result in defective ammonia metabolism, particularly in the liver, leading to accelerated accumulation of harmful amounts.[2]

In adults, hyperammonemia is primarily associated with conditions such as liver failure, particularly cirrhosis and acute liver failure, which may result in hepatic encephalopathy. Liver damage reduces urea cycle function, leading to decreased ammonia metabolism. Additionally, certain medications, such as valproic acid, in addition to kidney disease, may elevate ammonia levels.[3]

Increased ammonia concentrations are harmful to the central nervous system. Ammonia can traverse the blood-brain barrier, impacting energy metabolism in neuronal cells and leading to a decrease in ATP, the primary mol-

ecule for intracellular energy transfer. The process may lead to irreversible damage, especially in pediatric patients, manifesting as neurological symptoms such as lethargy, disorientation, and coma.[4] Increased ammonia levels disrupt glutamate metabolism in the brain, leading to excitotoxicity that damages neurons and results in neurotoxicity.[5]

As a result, hyperammonemia is a critical condition that requires urgent diagnosis and intervention, especially in pediatric metabolic diseases. Determination of blood ammonia levels, especially in patients presenting to neonatal and pediatric emergency departments with unexplained encephalopathy or neurological symptoms, is of great importance for the early diagnosis of potentially reversible metabolic disorders.

In this study, the reasons for measuring ammonia levels in pediatric patients at the hospital in the last five years were examined and their contributions to the diagnosis and treatment process of hyperammonemia were evaluated.

MATERIALS AND METHODS

The study was conducted by retrospectively examining hospital system data. The study started following the approval of the ethics committee. The study was approved by the Lütfi Kırdar City Hospital Ethics Committee (Approval date: 25.10.2024-Approval number: 2024/010.99/9/34). The research was conducted applying the hospital automation system records and patient records. The study was conducted in accordance with the Helsinki Declaration.

Patients under 18 years of age, for whom blood ammonia levels were requested in polyclinics and inpatient services within the Department of Pediatrics from October 1, 2020, to October 31, 2024, and the results were above 60 mmol/L were included in the study. Individuals aged 18 and above and the results under 60 mmol/L were excluded from the study.

The number of ammonia requests, the number of patients, ammonia levels, demographic characteristics, reasons for admission, and final diagnoses of the patients were recorded in the data collection form as study data.

Statistical Analysis

Data were analyzed with IBM SPSS V23. Compliance with normal distribution was examined with the Kolmogorov-Smirnov Test. Mann-Whitney U test was used to compare data that did not comply with normal distribution in pairs. Pearson chi-square test, Yates correction, and Fisher's Exact tests were used to examine the relationship between categorical data, and multiple comparisons were made with Bonferroni correction.

Table 1. Distribution of gender, age, diagnosis code, reason for test request and ammonia levels of patients for whom ammonia was requested in the pediatric clinic

	Average Deviation / Frequency	Median (min-max) / Percentage
Nationality		
Türkiye	401	95.9
Syrian	16	3.8
Iraq	1	0.2
Gender		
Male	236	56.5
Female	182	43.5
Diagnosis Code		
F82	151	36.3
E88.8	30	7.2
G40.9	30	7.2
Others	205	49.3
Test Request		
Seizure	124	30.6
Neuromotor retardation	64	15.8
Autism	46	11.4
Other	173	42.2
Age		
Under the age of 1 month	37	8.9
Above 1 month	381	91.4
Amonia level		
≤250 mmol/lt	393	94
>250 mmol/lt	25	6
Amonnia levels	126.03±130.72	87.84 (60.36-1235.46)
Age 4.51±6.69	2.5 (0.08-104.83)	

Mean±standard deviation and median (minimum-maximum) were used to display quantitative data. Frequency and percentage were used to display categorical data. The significance level was taken as $p<0.05$.

RESULTS

The study included 285 admissions among 255 patients who met the criteria and requested ammonia testing. One hundred forty-six (51.2%) of all admissions were male; the mean age was 67.2±69.7 months (Table 1).

A total of 1450 desired outcomes from 1080 patients were assessed. Among these, 420 patients had 556 results above 60 mmol/L, and the study included the results of these patients.

In this study, the demographic characteristics of 418 patients for whom ammonia tests were requested were analyzed. 95.9% (n=401) of the patients were Turkish nationals, 3.8% (n=16) were Syrian nationals, and 0.2% (n=1) was of Iraqi nationality. When analyzing the gender distribution, 56.5% (n=236) of the patients were male and 43.5% (n=182) were female. When the age distribution was examined, 8.9% (n=37) of the patients were in the newborn group aged 1 month and below, and 91.1% (n=381) were in the age group over 1 month. These data show that ammonia test requests are mostly made for boys of Turkish nationality, aged over 1 month (Table 1).

Gender distribution is similar between male and female patients: 56.5% of the patients are male (n=236) and 43.5% are female (n=182). This proportional distribution between genders reveals that there is no significant difference between male and female patients in the frequency of requesting ammonia testing.

The most common diagnosis code found with the ammonia test request was F82, which demonstrated up 36.3% of the time (n=15). Following this code, codes E88.8 and G40.9 both demonstrated up 7.2% of the time (n=30). People with alternative diagnosis codes represented 49.3% (n=205). According to this distribution, the number of requests for ammonia measurements is high, especially among children with diagnosis code F82 (neurodevelopmental disorders).

Upon investigating the reasons for requesting an ammonia test, it was observed that seizures (30.6%), neuromotor retardation (15.8%), autism diagnosis (11.4%), and other clinical reasons (42.2%) were the most frequently cited. Further, the most prevalent findings associated with testing orders are infection (25%), valproic acid use (47.5%), test error (hemolysis or prolonged waiting) (13.8%), and other factors. These data suggest that neurological symptoms and valproate use are significant factors in the motivations for requesting ammonia testing.

Neuromotor retardation (25%) was the most frequently requested reason for testing in patients aged 1 month and younger when grouped by age. Conversely, the group older than 1 month experienced an increase in test demand for reasons such as autism (12.2%) and seizures (31.4%). These age groups' distinct reasons for requesting testing indicate that the necessity of ammonia measurement is influenced by age-related clinical conditions.

The median ammonia value of patients in the 1 month and younger age groups was 85 µmol/L, whereas the value in the group aged over 1 month was 88.32 µmol/L. There was no statistically significant difference in ammonia value depending on age ($p=0.564$). The median ammonia value was 86.38 µmol/L in male patients and 89.25 µmol/L in females when evaluated according to gender. A statistically significant difference between gender and ammonia value was not observed ($p=0.216$). These results indicate that ammonia levels do not vary significantly by age and gender variables (Fig. 1).

The ammonia values were examined in two groups: ≤250 µmol/L and >250 µmol/L. 94% of the patients (n=393) had an ammonia value below 250 µmol/L, while 6% of the patients (n=25) had an ammonia value above 250 µmol/L. The majority of patients showed ammonia levels that were within the normal range, with only a small number of patients having pathological levels (Fig. 2).

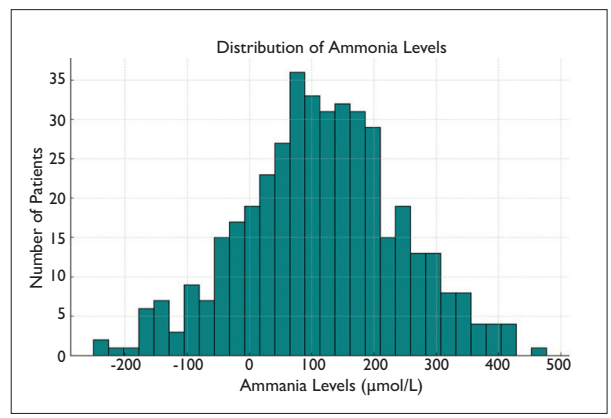

Figure 1. Distribution of ammonia levels.

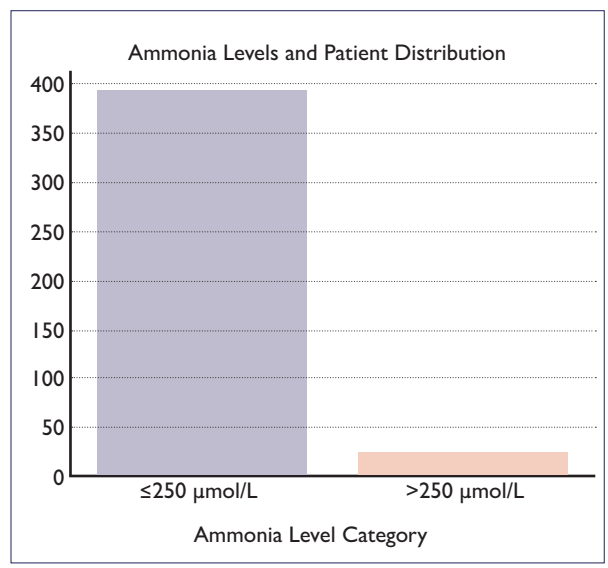

Figure 2. Ammonia Levels and patient distribution.

DISCUSSION

The clinical and demographic characteristics of pediatric patients who submitted inquiries for ammonia testing at the hospital were investigated in this study. The findings emphasize significant differences in reasons for ammonia testing based on age, particularly when contrasting infants under one month of age with older children.

Ammonia testing is primarily requested in neonates to diagnose metabolic disorders, including organic acidemias and urea cycle defects. In this age group, hyperammonemia is frequently associated with inherited metabolic diseases (IMDs), which may result in life-threatening symptoms such as lethargy, seizures, and coma. Ammonia can accumulate rapidly in newborns because of their immature metabolic pathways, requiring early testing. In cases of suspected IMDs in the neonatal period, Kadıoğlu Yılmaz et al.[6] also observed a higher frequency of ammonia test requests.

Ammonia testing is more frequently associated with acquired conditions in children over one month of age, such as liver dysfunction, medication effects, and infections. The literature underlines that valproate-induced hyperammonemia is a prevalent etiology in older children who have gone through antiepileptic therapy. Valproate may result in elevated ammonia levels, which require monitoring to avoid neurotoxic effects, by inhibiting the urea cycle. This is consistent with our research, which demonstrated that valproate was a significant contributor to hyperammonemia in patients over one month of age.[7]

Ammonia testing was requested for 30.6% of the cases in our study due to neurological symptoms, such as seizures and abnormal mental conditions. This is in line with the results of Ali and Nagalli (2023), who highlight the importance of hyperammonemia in neurotoxicity as a result of its capacity to disrupt neurotransmitter balance and cross the blood-brain barrier. Consequently, ammonia testing is essential in the diagnostic method for pediatric patients who exhibit unexplained neurological symptoms.[8]

Ammonia levels are also significantly influenced by age, with neonates having naturally higher baseline levels as a result of their immature liver function. Our research confirmed the findings of Ribas et al.[9] that ammonia levels were generally in the lower range for older children, which is suggestive of the maturing of metabolic processes with age.

The high frequency of misleading results in ammonia testing is another important discovery in our study. This phenomenon can be influenced by pre-analytical factors such as sample handling and transport conditions. Maranda et al.[10] demonstrated that clinical decisions can be influenced by falsely elevated ammonia levels resulting from improper sample handling. It is essential to implement rigorous sample processing protocols in order to reduce the likelihood of inaccurate results.

This study has several limitations that must be considered when interpreting the results:

• The study is retrospective, depending on historical records and data. Prospective studies may facilitate more regulated data collection and standardized protocols.

• The data was obtained from a singular institution, potentially limiting the generalizability of the findings to other hospitals or regions. Multi-center studies might provide diverse data and comprehensive insights into ammonia testing practices across diverse pediatric populations and healthcare settings.

• Some patient subgroups, especially those with rare illnesses or specific etiologies for hyperammonemia, showed only a small number of cases.

• Sample handling, transport, and processing affect ammonia levels. Despite efforts to reduce errors, sample processing delays and improper storage may have caused ammonia measurements to be inaccurate. This may affect the study's hyperammonemia prevalence.

• This study focused on establishing ammonia testing frequencies and associated clinical characteristics but did not conduct a longitudinal follow-up of patients to evaluate outcomes associated with hyperammonemia. As a result, we cannot assess the effect of the measured ammonia levels on long-term patient health or treatment efficacy.

• The study provides facts about the clinical characteristics of patients undergoing ammonia testing; however, it fails to consider all potential confounders, such as underlying comorbidities and concurrent medications, which may have affected ammonia levels. A more thorough analysis with controlled variables may produce additional conclusions.

• Ammonia reference values can differ significantly with age, and there is no generally accepted threshold for hyperammonemia in different pediatric age categories. The absence of standardization may influence the interpretation of ammonia levels and could introduce variability in the assessment of hyperammonemia across various age groups.

Recognizing these limitations allows for the design of future studies that may involve prospective, multicenter approaches with standardized sample handling protocols and extended follow-up to more accurately evaluate clinical outcomes associated with ammonia levels in pediatric patients.

Conclusion

This study emphasizes the importance of ammonia testing in pediatric patients, particularly in the detection of metabolic disorders in neonates and the management of drug-induced hyperammonemia in older children. The findings, despite their retrospective, single-center design, highlight the necessity of age-specific guidelines and standardized protocols in ammonia testing. Future research using longitudinal follow-ups and multicenter data may provide more information, helping clinicians to enhance diagnostic accuracy and improve patient outcomes related to hyperammonemia.

Ethics Committee Approval

The study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 25.10.2024, Decision No: 2024/010.99/9/34).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: E.Ö.E., B.Y.; Design: E.Ö.E., B.Y.; Supervision: Y.A.; Fundings: Y.Ç., Y.A.; Data collection &/or processing: B.Y.; Analysis and/or interpretation: E.Ö.E., B.Y.; Literature search: E.Ö.E., Y.Ç.; Writing: E.Ö.E., B.Y.; Critical review: Y.A.

Conflict of Interest

None declared.

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Son 5 Yılda Pediatri Kliniğinde Amonyak Test İstemi Nedenlerinin Araştırılması

Amaç: Amonyak, protein metabolizması sonucunda oluşan nörotoksik bir bileşiktir, karaciğerde üreye dönüştürülür ve böbreklerle atılır. Yenidoğan dönemi dışında 60 µmol/L'yi aşan değerler hiperamonyemi olarak değerlendirilir. Çocuklarda genetik ve metabolik durumlar, ilaç kullanımı; erişkinlerde ise karaciğer hastalığı veya ilaç kullanımı en sık hiperamonyemi nedenleridir.

Gereç ve Yöntem: Tek merkezli retrospektif çalışmamızda, son 5 yılda hastanemizde bakılıp 60 µmol/L'yi aşan hasta sonuçları değerlendirildi. Hastaların yaş, cinsiyet, amonyak değerleri ve amonyak istenme nedenleri incelendi.

Bulgular: Bu çalışmada, hastanemizde pediatrik hastalarda amonyak testi isteme nedenleri incelenmiştir. Bulgular, 1 ay altı ve üstü çocuklar arasında test isteme nedenlerinde farklılıklar olduğunu göstermiştir. Yenidoğanlarda testler genellikle metabolik bozukluklar için yapılırken, 1 ay üstü çocuklarda karaciğer fonksiyon bozuklukları, ilaç yan etkileri ve enfeksiyonlar ön plandadır. Çalışmanın retrospektif tasarımı ve tek merkezli olması ise önemli sınırlamalar olarak belirtilmiştir.

Sonuç: Pediatrik hastalarda nörolojik hastalıkları temelinde hiperamonyemi olabileceği gibi nöbet nedeni ile kullanılan ilaçlar da hiperamonyemiye neden olabilir. Bu durum nöbetle başvuran, özellikle bilinç durum değişikliği olan hastalarda akılda tutulmalıdır.

Anahtar Sözcükler: Amonyak; epilepsi; hiperamonyemi; nöromotor retardasyon; otizm.