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ORIGINAL ARTICLE

Evaluation of the Frequency of Blood Ammonia Test Requests in Clinic of Pediatrics Before and After the Establishment of the Department of Pediatric Metabolism

Pediatri Kliniklerinde Kan Amonyak Tetkiki İstenme Sıklığının Çocuk Metabolizma Bölümü Açılması Öncesinde ve Sonrasında Değerlendirilmesi

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ABSTRACT

Background/Aims: Hyperammonemia causes severe mortality and morbidity when left unnoticed. We aimed to compare the number of ammonia test requests before and after establishing the Department of Pediatric Metabolism (DPM) in a clinic of pediatrics.
Methods: The study was conducted retrospectively between 15/11/2022-16/11/2023. Study data were evaluated before (pre-group) and after (post-group) the establishment of DPM.
Results: Two hundred eighty-five admissions were assessed in the study. There were 99 admissions in the pre-group and 186 in the post-group. There were 17 admissions for different reasons in the pre-group and 29 in the post-group. The most common reasons for admission were elevated transaminases, seizures, vomiting and metabolic acidosis. Definitive diagnosis was made in 16 (17.6%) patients admitted in the pre-group and 39 (23.8%) in the post-group. The most common diagnoses were genetic syndromes, mitochondrial diseases and organic acidemias. Twenty-one patients were diagnosed with inherited metabolic diseases (IMDs). Mitochondrial diseases were the most commonly diagnosed IMD (8(38%)). From the 15 pediatric subunits, ammonia test was requested from 8 in the pre-group and 13 in the post-group. In the pre-group, the pediatric subunit where ammonia was requested the most was the Pediatric Neurology Polyclinic (n=25 (25.3%)). In the post-group, the subunit that required the highest number of ammonia tests was the DPM (68(23.9%)). In the ROC analysis conducted for the predictive power of the initial ammonia level in requesting a control ammonia test, the area under the curve is 0.927, and the p-value is 0.001. For the cut-off value of 60.3 µmol/l, the sensitivity was 90.9%, and the specificity was 88.6%.
Conclusion: After DPM was established, there was an increase in ammonia test requests, in the diversity of reasons for requesting ammonia testing from admissions, and in IMD diagnosis. DPM had a positive effect on pediatricians' awareness of hyperammonemia.

Keywords: Hyperammonemia, Ammonia, Inherited metabolic diseases, Pediatrics

ÖZ

Amaç: Hiperamonyemi, fark edilmediğinde ciddi mortalite ve morbiditelere neden olur. Bir pediatri kliniğinde, Çocuk Metabolizma Hastalıkları kliniği (ÇMHK) açılmadan öncesi ve sonrası amonyak istem sayılarının karşılaştırılmasını amaçladık.
Yöntem: Çalışma, 15/11/2022-16/11/2023 tarihleri arasında retrospektif olarak gerçekleştirildi. ÇMHK kurulmasına göre öncesi ve sonrası olarak çalışma verileri değerlendirildi.
Bulgular: Çalışmada 285 başvuru değerlendirildi. Öncesi grupta 99, sonrası grupta 186 başvuru vardı. Öncesi grupta 17, sonrası grupta 29 farklı nedenle başvuru oldu. En sık başvuru nedenleri; transaminaz yüksekliği, nöbet, kusma ve metabolik asidozdu. Öncesi grupta başvuran hastaların 16 (%17,6)'sına, sonrası gruptaysa 39 (%23,8)'una tanı konuldu. En sık tanılar; genetik sendromlar, mitokondriyal hastalıklar ve organik asidemilerdi. 21 hastaya kalıtsal metabolik hastalık (KMH) tanısı konuldu. En çok tanı konulan KMH, mitokondriyal hastalıktı (8 (%38)'i). 15 pediatri alt biriminin öncesi grupta 8, sonrası grupta 13'ünden amonyak tetkiki istendi. Öncesi grupta en çok amonyak istenen pediatri alt birimi Çocuk Nöroloji Polikliniğiydi (n=25 (%25,3)). Sonrası grupta en fazla amonyak istenen alt birim ÇMHK'ydi (68(%23,9)). İlk amonyak düzeyinin kontrol amonyak tetkiki istemedeki kestirim gücü için yapılan ROC analizinde eğri altında kalan alan 0,927, p değeri 0,001'dir. Kestirim değeri 60,3 µmol/l için duyarlılık %90,9, özgüllük %88,6 saptandı.
Sonuç: ÇMHK kurulduktan sonra, amonyak testi istemlerinde, amonyak testi istenen başvurulardaki çeşitlilikte ve KMH tanılarında artış saptandı. ÇMHK, pediatristlerin hiperamonyemi farkındalığı üzerine olumlu etkiye sahipti.

Anahtar kelimeler: Hiperamonyemi, amonyak, kalıtsal metabolik hastalıklar, pediatri

Introduction

Ammonia is a neurotoxic molecule formed due to the breakdown of amino acids in the protein structure and is also produced by bacteria in the intestinal flora (1). Ninety percent of the ammonia produced in the body is transported to the periportal hepatocytes by the portal circulation, where it is converted to urea via the urea cycle pathway and excreted in the urine (1). Ten percent of ammonia, a water-insoluble molecule

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that does not enter the urea cycle, is transported to perivenous hepatocytes and converted from glutamate to glutamine by the enzyme glutamine synthase (2). Glutamine is used as energy or excreted in urine (2). In the case of hyperammonemia, which develops due to increased production or decreased elimination of ammonia, ammonia passes from the portal circulation to the systemic circulation (3). It reaches the brain, causing severe neurological findings with its neurotoxic effect (3).

Hyperammonemia is defined as the ammonia level above 80 µmol/L in infancy and 55 µmol/L in older children (4). However, there are different threshold values in different sources (5). Clinical findings of hyperammonemia are nausea, vomiting, anorexia, growth retardation, neuropsychiatric symptoms, headache, ataxia, dysarthria, behavioral changes, neurodevelopmental retardation, hypotonia, seizure, changes in consciousness, coma and central hyperventilation (1). It may present with sepsis-like clinical conditions, especially in the neonatal period (1). The ammonia level should be checked in cases that exhibit a wide range of clinical findings and in every child with undiagnosed neurological findings (3,4).

Hyperammonemia is caused by inherited metabolic diseases (IMDs) caused by enzyme deficiency and genetic disorders (urea cycle disorders, organic acidemias, lysinuric protein intolerance, carbonic anhydrase VA deficiency, pyruvate carboxylase deficiency, fatty acid oxidation defects), acute or chronic liver diseases, medications (valproic acid, cyclophosphamide), portosystemic shunt and conditions that lead to protein catabolism (5).

In addition to various diseases in the etiology of hyperammonemia, false positive results are also high due to pre-analytical situations (6). A study in the literature found that 48% of 1880 ammonia measurements from 479 patients had false positive high results (6). Conditions that cause false positive ammonia levels: It is the release of ammonia from the lysis of erythrocytes after blood collection, the formation of ammonia as a result of the deamination of amino acids in the plasma, the tourniquet applied during blood sample collection and the transport temperature of the sample (6-8). Such false positive results may also negatively influence clinicians' orders for ammonia testing.

While the majority of the causes of hyperammonemia in adults are cirrhotic liver diseases, in children, IMDs, especially urea cycle disorders and organic acidemias, come to the fore (9-11). Although IMDs are prominent in the etiology of hyperammonemia in children, diseases in this group are still considered among the "rare diseases." The incidence of urea cycle disorders is reported as 1/35,000, organic acidemias are 1/3000 and fatty acid oxidation defects are 1/9000 (11-12). Although the incidence of an IMD may seem "rare" when viewed individually, the number of IMDs identified by developing genetic studies is increasing yearly (13). Considering all IMDs, the incidence of being diagnosed with a metabolic disease is between 1/800 and 1/2500 and is not rare (13).

For this reason, these diseases do not often come to mind in clinical practice, except for Pediatric Metabolism specialists and other specialists specifically interested in IMDs. However, there are still many admissions to all clinic of pediatrics with symptoms of hyperammonemia (nausea, vomiting, loss of appetite, growth retardation, neuropsychiatric symptoms, headache, ataxia, dysarthria, behavioral changes, neurodevelopmental retardation, hypotonia, seizures, changes in consciousness).

This study aims to compare the number of ammonia test requests from patients admitted to clinic of pediatrics for the period of six months before and after the Department of Pediatric Metabolism (DPM) was established in a university hospital. This comparison was planned to reveal the hyperammonemia awareness level in the clinic of pediatrics and the characteristics of the patient groups whose ammonia levels were measured.

Material and Methods

Study design and settings

This study was conducted retrospectively with second-grade students within the scope of the Selçuk University Faculty of Medicine, Evidence-Based Medical Practices program. It was started after receiving ethics committee approval (Selçuk University Faculty of Medicine Local Ethics Committee; No: 2023/591, Date: 19/12/2023). The study was carried out using the hospital automation system records and patient file information. Patients under the age of 18 whose blood ammonia level was requested in the polyclinics and inpatient services under the Department of Pediatrics between November 15, 2022, and November 16, 2023 were included in the study. Patients over the age of 18, pregnant women, and patients requiring ammonia in internal and surgical medicine branches other than pediatrics were excluded from the study. Since the Department of Pediatric Metabolism was established in May 2023 and patient admission started on May 16, 2023, six months before the establishment of the Department of Pediatric Metabolism (November 15, 2022-May 15, 2023) was considered as the "pre-group" in the study. The six months after the clinic's establishment (May 16, 2023-November 16, 2023) was defined as the "post-group". In addition, all polyclinics and inpatient service units within the Department of Pediatrics were examined under 15 headings. These units were evaluated in 4 categories: polyclinic, inpatient services, intensive care units, and emergency department according to the medical care the patients received as outpatient or inpatient. The number of ammonia requests, ammonia levels, sample rejection numbers, the number of control ammonia requests from the same patient, demographic characteristics, reasons for admission and final diagnoses of the patients were recorded in the data collection form as study data.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 for

Windows. Descriptive criteria, mean and standard deviation, median and minimum and maximum values were presented as percentage distribution. The suitability of the data for normal distribution was checked with the Kolmogorov-Smirnov test. Student-t-test was used to compare continuous variables and chi-square analysis was used to compare distributions. ROC analysis was employed to examine the significance of the first ammonia test result in predicting the second test intake. 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).

Table 1. Comparison of study data before and after the establishment of the Department of Pediatric Metabolism

	Pre-group	Post-group	Total	
	Mean ± Standard Deviation (mean±SD)	Mean ± Standard Deviation (mean±SD)	Mean ± Standard Deviation (mean±SD)	p value
Age (month)	71.9±76.8	64.7±65.7	67.2±69.7	0.403*
Ammonia level (µmol/l)	46.49±51.18	47.36±36.92	47.06±42.33	0.869*
Presence of sample rejection	0.05±0.22	0.07±0.38	0.06±0.33	0.935**
	Number (Percentage) n (%)	Number (Percentage) n (%)	Number (Percentage) n (%)	
Gender				
Male	64 (64.6)	82(44.1)	146 (51.2)	0.001***
Female	35(35.4)	104(55.9)	139 (48.8)	
Ammonia level (µmol/l)				
Ammonia level <60 µmol/l	84 (84.8)	151 (81.2)	235 (82.5)	0.439***
Ammonia level >60 µmol/l	15 (15.2)	35 (18.8)	50 (17.5)	
Treatment Place				
Polyclinic	56 (56.6)	108 (58.1)	164 (57.5)	0.075***
Service	11 (11.1)	35 (18.8)	46 (16.1)	
Intensive Care Unit	13 (13.1)	25 (13.4)	38 (13.3)	
Emergency Service	19 (19.2)	18 (9.7)	37 (13.1)	
Sample rejection				
Number of sample rejection	5 (5.1)	9 (4.8)	14 (4.9)	0.937***

* Student t-test,**Mann Whitney-U test, ***Chi-Square test

When all admissions were evaluated, 99 (34.7%) ammonia test requests were in the pre-group, 186 (65.3%) were in the post-group, and 68 (23.9%) were requested from the DPM in the post-group (Figure 1).

The mean value for ammonia in all admissions was 47.06 ± 42.33 µmol/l. There was no statistically significant difference detected between the groups for mean ammonia values (p=0.869) distribution of patients according to inpatient or outpatient treatment services (p=0.075), presence of sample rejection (p=0.935), and the number of sample rejections (p=0.937). The high ammonia value (>60 µmol/l) was detected in 15.2% of the pre-group and 18.8% of the post-group (Table 1).

The distribution of the patient's reasons for admission in the pre-group and post-group is shown in Figure 2. It was determined that they were admitted for 17 different reasons in the before group and for 29 different reasons in the post group. The four most common reasons for admission were elevated transaminase (37 [37.4%] in the pre-group, 53 [28.5%] in the post-group), seizure (12 [12.1%] in the pre-group, 26 [14%] in the post-group), vomiting (11 [11%] of the pre-group, 10 [5.4%] of the post-group) and metabolic acidosis (3 [3%] of the pre-group, 13 [7%] of the post-group).

A definitive diagnosis was made in 16 (17.6%) of the patients admitted in the pre-group and in 39 (23.8%) in the post-group. The most common diagnoses were genetic syndromes [2 (2.2%) of the patients in the pre-group, 7 (4.3%) in the post-group], mitochondrial diseases [2 (2.2%) of the patients in the pre-group, 6 (%3.7) in the post group] and organic acidemias [7 (4.3%) of the patients admitted in the post-group]. At the same time, it was not detected in the pre-group) (Figure 3a). A total of 21 patients were diagnosed with IMD. Mitochondrial diseases were the most commonly diagnosed IMD (8 [38%]). All organic acidemias were diagnosed in the post-group, and it was the second most diagnosed IMD (7 [33.8%]). There was one patient diagnosed with hereditary fructose intolerance and congenital glutamine deficiency, and they were diagnosed in the post-group (Figure 3b).

The distribution of admissions requiring ammonia testing in the pre-group and post-group from the pediatric subunits is shown in Figure 4. There were 15 subunits under the roof of the Department of Pediatrics. Ammonia tests were requested from 8 of the 15 pediatric subunits in the pre-group and 13 in the post-group. In the pre-group, the pediatric subunit where ammonia tests were requested most frequently was the Pediatric Neurology polyclinic (n=25 [25.3%]). Pediatric Metabolism polyclinic was the subunit with the highest number of ammonia test requests in the post-group (68 [23.9%]). While there was no ammonia request in the pre-group from the General Pediatrics service, there were 11 ammonia requests in the post-group. In addition, it was observed that there was an approximately two-fold increase in the number of ammonia test requests in the Pediatric Gastroenterology service and Pediatric Intensive Care subunits in the post-group.

There were 50 admissions with an initial ammonia value >60 µmol/l. The mean ammonia level of these admissions was 109.2 ± 69.9 µmol/l (min: 60.4 µmol/l, max: 413.5 µmol/l). A repeat ammonia test was requested from 20 of 50 admissions (40%) whose initial ammonia value was found to be over 60 µmol/l. Even though the first value was above 60 µmol/l in 30 (60%), a repeat ammonia test was not requested. Of the 50 admissions whose first ammonia value was over 60 µmol/l, a second ammonia test was requested from 9, a third from 5, a fourth from 5, and a fifth from 1. The mean time to request a second repeat ammonia test was 43.1 ± 60.2 hours (min: 1.5 max: 228.0).

The ROC analysis was conducted to determine the predictive power of the initial ammonia level in requesting a control ammonia test, which had an area under the curve of 0.927 and a p-value of 0.001. When the cut-off value was taken above 60.3 µmol/l, the sensitivity was found as 90.9%, and the specificity was 88.6% (Figure 5).

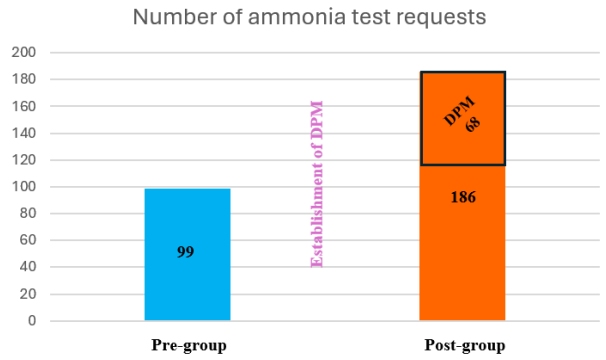

Figure 1. Comparison of ammonia test request numbers in groups before and after the establishment of DPM.

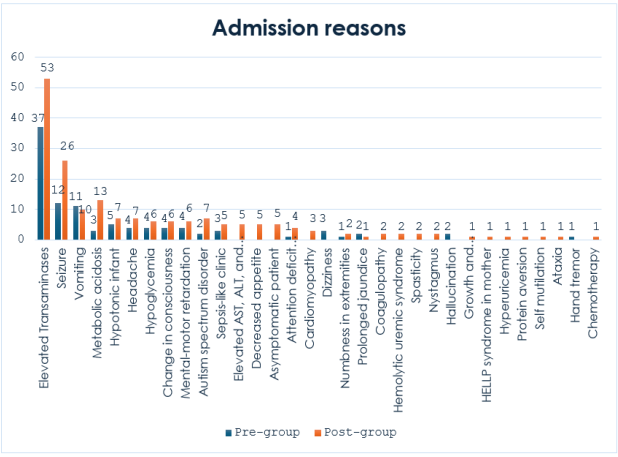

Figure 2. Comparison of admission reasons in groups before and after the establishment of DPM.

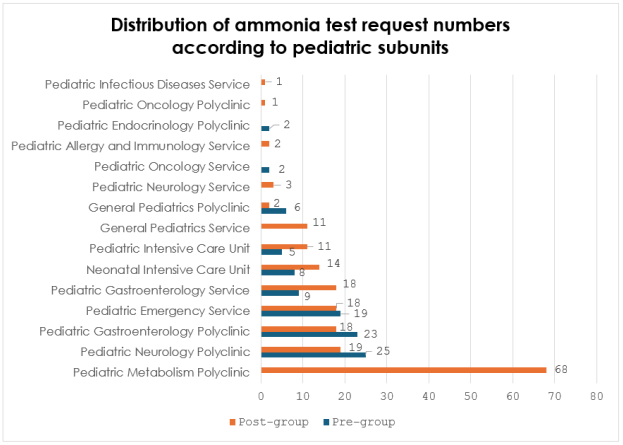

Figure 4. Distribution of ammonia test request numbers according to pediatric subunits

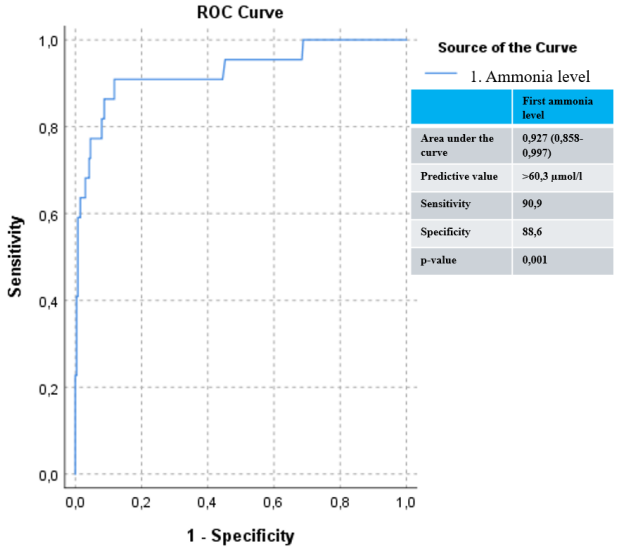

Figure 5. The ROC analysis to determine the predictive power of the initial ammonia level in requesting a control ammonia test.

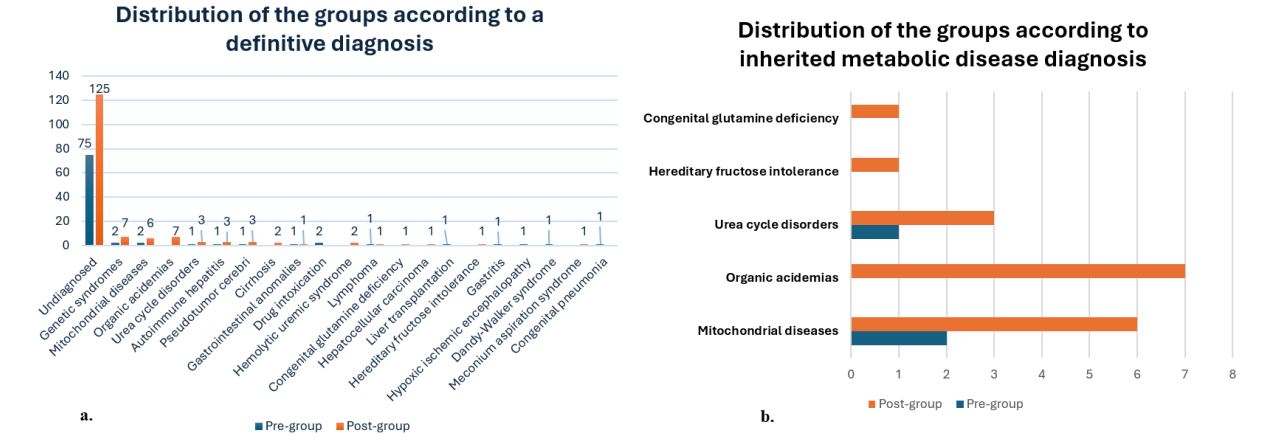

Figure 3. Distribution of definitive diagnosis and inherited metabolic diseases diagnosis between groups. a; distribution of the groups according to a definitive diagnosis, b; distribution of the groups according to inherited metabolic disease diagnosis.

Discussion

IMDs are mostly inherited as autosomal recessive and can be diagnosed at any age from the neonatal period to adulthood (14-16). Studies have shown that in the diagnosis of IMDs, it is essential to determine the clinical and biochemical phenotypes of the cases (rhabdomyolysis, hyperammonemia, myelopathy, etc.) and then to associate the phenotype in the cases with specific IMD and that suspecting the disease is vital in the diagnosis, and that it is beneficial to consult a metabolism specialist after a preliminary diagnosis is made. (15,16). As IMDs have begun to be diagnosed more frequently in our country and around the world, there is a need for physicians specialized in this field, which leads to the emergence of a DPM that deals with these diseases (16). Our study evaluated the period before and after the DPM in terms of hyperammonemia. We investigated the effect of this branch of science on pediatricians' awareness of hyperammonemia.

In our study, it was found that after the establishment of the DPM, more ammonia tests were requested, more ammonia tests were requested for different reasons at admissions, more patients were diagnosed, and more patients were diagnosed with IMD. It is mentioned in the literature that physicians lack knowledge and experience about IMDs and avoid the diagnosis and treatment process of these diseases such as hyperammonemia and metabolic acidosis, which should be considered in the differential diagnosis (16). In our study, the increase in the diversity of hyperammonemia admissions and the increase in ammonia requests and diagnosed patients showed that the awareness of hyperammonemia among pediatricians has increased. The DPM may not only raise awareness of rare diseases in other pediatric subunits but also alleviate the hesitation of pediatricians in the diagnosis and follow-up of IMD.

Our study found that patients admitted to pediatric subunits had 29 different signs and symptoms of hyperammonemia. The most common reasons for admission were elevated transaminases, seizures, vomiting and metabolic acidosis, respectively. It has been reported in the literature that hyperammonemia does not have specific signs and symptoms and can present with a wide variety of clinical conditions such as unexplained vomiting, seizures and unexplained neurological findings (17-19). It was similar to the literature that patients applied for many different reasons and that admissions were due to seizures, vomiting and metabolic acidosis. However, the fact that elevated transaminase levels is the most common reason for admission in more than 1/3 of the patients is different from the literature. Hyperammonemia and elevated transaminase levels coexistence is more common in cirrhosis (17). This may be because pediatric gastroenterology polyclinics and service units are among the pediatric subunits most frequently requiring ammonia tests after pediatric metabolism polyclinics.

The etiology of hyperammonemia, a symptom of many congenital and acquired disorders due to hepatic or nonhepatic reasons, is very diverse (11,17,20,21). Its etiology includes urea cycle defects, including enzymatic defects, organic acidemias, congenital lactic acidosis, mitochondrial fatty acid oxidation defects, and dibasic amino acid deficiencies, as well as other disorders such as transient hyperammonemia of the newborn, neonatal Herpes simplex virus (HSV) infection, cirrhosis, malignancy, and severe perinatal asphyxia. (17,22). This situation may have caused more than one clinic to evaluate the patient together, thus requiring more ammonia tests in service patients during the diagnosis and treatment. In our study, the fact that genetic syndromes, mitochondrial diseases, organic acidemias, and urea cycle defects were the most common diagnoses in patients presenting with signs and symptoms of hyperammonemia shows that although IMDs are defined as rare diseases, they are not very rare and should be considered in the differential diagnosis of hyperammonemia.

The limited number of sample rejections in both periods in the study showed that laboratory and healthcare workers were aware of situations that could cause erroneous results in the ammonia test, such as blood collection by tightening with a tourniquet, not transporting the sample at optimal temperature (with an ice tray), and running the test late because the reliability of ammonia testing requires strict standardization from blood collection to transportation to the laboratory and the process of working in the laboratory (23).

Hyperammonemia is a severe clinical condition that causes mortality and morbidity in patients (20). Therefore, in treating acute hyperammonemia, reducing the ammonia level and controlling specific complications such as cerebral edema and intracranial hypertension are the most critical issues (17). To reduce circulating ammonia, protein intake is stopped, and calories are provided with glucose infusions (17). Hemodialysis should be considered in cases where ammonia must be removed rapidly (24,25). Additionally, sodium benzoate and phenylacetate compounds, which convert nitrogenous residues into non-urea components, are used in IMDs (25). Oral non-absorbable disaccharides (such as lactulose) are used for hepatic encephalopathy secondary to hyperammonemia. These sugars reduce the production and absorption of ammonia in the intestine (26). The patient's clinical findings and control ammonia levels should be closely monitored to evaluate the response to treatment (11,17,20,22,24).

In our study, out of 50 admissions whose first ammonia value was found over 60 µmol/l, an ammonia test was requested from 9 of them for the 2nd time, 5 of them for the 3rd time, 5 of them for the 4th time, and 1 of them for the 5th time. In addition, when the predictive value of the initial ammonia level for requesting a control ammonia test was taken above 60.3 µmol/l, the sensitivity was 90.9%, and the specificity was 88.6%. This revealed that pediatricians closely monitor the

ammonia level higher than 60.3 µmol/l in patients presenting with hyperammonemia, both in diagnosis and treatment follow-up and request a control ammonia test above this value.

There were some limitations in our study. A limitation is that the study is retrospective and conducted as an archive scan. Another limitation is that we did not evaluate the clinical outcomes of the patients. Although this is an issue we did not address because our study was not a mortality study, it prevented us from commenting on the relationship between ammonia levels and clinical outcomes. Since the study was not conducted prospectively, we cannot discuss standardization or what criteria physicians consider when ordering ammonia tests. In this case, it is an important limitation as it will prevent the randomization of the study.

Conclusion

In our study, we found that after the DPM was established, ammonia tests were requested by pediatricians from more patients who came for different reasons, more patients were diagnosed, and the number of patients diagnosed with IMD increased. Our study revealed that pediatricians should pay attention to the ammonia level of 60.3 µmol/l when requesting a control ammonia test to diagnose and follow up hyperammonemia. All these indicators showed that the Department of Pediatric Metabolism positively impacted pediatricians' awareness of hyperammonemia.

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Author Contributions: Conceptualization, Data curation, and Formal Analysis: B.K.Y.; Investigation: B.K.Y., İ.A.A.J.A., F.R., M.E.G., A.S.Y., Z.A.T., S.A., S.N.A., Y.E.E., İ.S., S.G., E.Ç., M.E.Ö., E.E., B.N.E.; Methodology: B.K.Y., İ.A.A.J.A., F.R., M.E.G., A.S.Y., Z.A.T., S.A., S.N.A., Y.E.E., İ.S., S.G., E.Ç., M.E.Ö., E.E., B.N.E.; Supervision: B.K.Y.; Validation: B.K.Y.; Writing-original draft: B.K.Y., İ.A.A.J.A., F.R., M.E.G., A.S.Y., Z.A.T., S.A., S.N.A., Y.E.E., İ.S., S.G., E.Ç., M.E.Ö., E.E., B.N.E.; Writing-review and editing: B.K.Y., İ.A.A.J.A., F.R., M.E.G., A.S.Y., Z.A.T., S.A., S.N.A., Y.E.E., İ.S., S.G., E.Ç., M.E.Ö., E.E., B.N.E. All authors have read and agreed to the published version of the manuscript.

Ethical Approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Selçuk University Faculty of Medicine Local Ethics Committee (Decision No: 2023/591, Date: 19/12/2023).

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