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Original Article

Comparison of Knowledge Levels and Attitudes of Family Medicine Assistants About Meningococcal Infection and Vaccines Before and After Education

Aile Hekimliği Asistanlarının Meningokok Enfeksiyonu ve Aşıları Hakkında Bilgi Düzeyleri ve Tutumlarının Eğitim Öncesi ve Sonrası Karşılaştırılması

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ABSTRACT

Objective: *Neisseria meningitidis*, which has one of the highest mortality rates without treatment, is one of the most common causes of bacterial meningitis in the world. Invasive meningococcal disease caused by this agent is one of the diseases that can be prevented by vaccination. The aim of this study was to measure and evaluate the level of knowledge and attitudes of family medicine residents about meningococcal infection and vaccines before and after the training program.

Material and Methods: Our descriptive cross-sectional study was conducted between 01.02.2023 and 31.03.2023 with 102 family medicine residents working in University of Health Sciences Türkiye, Adana City Training and Research Hospital, Participants were asked for sociodemographic data before and after the training program and questionnaire about their knowledge and attitudes about meningococcal infection and vaccines. The data obtained were analyzed with a statistical software package.

Results: The median age of the 102 participants was 31 years. Among the participants, 56.9% were women; 31.4% had encountered patients with meningococcal infection during their professional life; 29.4% had sufficient knowledge about the vaccine; 89.2% stated that they would have their own children vaccinated; 95.1% thought that it should be included in the Expanded Programme on Immunization (EPI); and 94.1% recommended that families have their children vaccinated. There was a significant difference between the pre-test and post-test mean scores of the level of knowledge about meningococcal infection and vaccines ($p<0.05$).

Conclusion: Primary prevention is a vital aspect of family medicine. High mortality and morbidity associated with vaccine-preventable meningococcal disease, and newly developed vaccines should be emphasized in the content of the training titled "non-EPI vaccines" in the residency program.

Keywords: Meningococcus, vaccine, meningitis

ÖZ

Amaç: Tedavisiz mortalite oranı en yüksek bulaşıcı hastalıklardan olan *Neisseria meningitidis,* dünyadaki bakteriyel menenjitin en yaygın nedenlerinden biridir. Bu etken nedeniyle ortaya çıkan invazif meningokok hastalığı aşı ile önlenebilen hastalıklardandır. Bu çalışmadaki amacımız; düzenlenen eğitim programı öncesi ve sonrası aile hekimliği asistanlarının meningokok enfeksiyonu ve aşıları hakkında bilgi düzeyleri ve tutumlarını ölçmek ve değerlendirilmektir.

Gereç ve Yöntemler: Çalışmamız tanımlayıcı kesitsel tipte olup 01.02.2023 ile 31.03.2023 tarihleri arasında Sağlık Bilimleri Üniversitesi, Adana Şehir Eğitim ve Araştırma Hastanesi'nde çalışan 102 aile hekimliği uzmanlık öğrencisi ile gerçekleştirilmiştir. Katılımcılara eğitim programı öncesi ve sonrası sosyodemografik veriler ile meningokok enfeksiyonu ve aşıları hakkında bilgi ve tutumlarına yönelik hazırlanmış anket soruları yöneltilmiştir. Elde edilen veriler istatistiksel paket program ile analiz edilmiştir.

Bulgular: Çalışmaya katılan 102 katılımcının ortanca yaş değeri 31'idi. Katılımcılardan kadınların oranı %56,9; meslek hayatı boyunca meningokok enfeksiyonlu hasta ile karşılaşmış olanların oranı %31,4; meningokok aşısıyla ilgili yeterli bilgiye sahip olanların oranı %29,4;

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ÖZ

kendi çocuğuna meningokok aşısı yaptıracağını belirtenlerin oranı %89,2; meningokok aşısının Genişletilmiş Bağışıklama Programı'nda (GBP) olması gerektiğini düşünenlerin oranı %95,1; ailelere çocuklarına meningokok aşısı yaptırmalarını önerenlerin oranı %94,1'dir. Meningokok enfeksiyonu ve aşıları bilgi düzeyi ön test ve son test puan ortalamaları arasında anlamlı farklılık saptandı (p<0,05).

Sonuç: Meningokok aşıları henüz GBP'de yer almamaktadır. Birincil koruma aile hekimliğinin en önemli etkinlik alanıdır ve asistanlık eğitimlerinde GBP dışı aşılar başlıklı eğitim içeriğine mortalite ve morbiditesi yüksek ve aşı ile korunulabilen meningokok hastalığı ve yeni geliştirilen aşılar vurgulanmalıdır.

Anahtar Kelimeler: Meningokok, aşı, menenjit

INTRODUCTION

Family physicians assume responsibility for community health as well as individual health, and immunization with vaccines, one of the primary prevention steps, is an important step in this special responsibility (1). They can monitor their registered population in terms of risk factors and exposures while they are not yet ill and before they apply to health institutions. With this lifelong follow-up and the relationship of trust established through recurring contacts, family physicians offer unique opportunities for immunization.

Meningococcal disease is a serious infectious disease caused by the bacterium *Neisseria meningitidis*. Clinical manifestations of meningococcal disease can range from asymptomatic carriage to invasive disease. *Neisseria meningitidis* causes various meningococcal disease pictures including bacteremia, meningococcemia, meningitis and chronic infection without sepsis and can also result in arthritis, pneumonia, occult bacteremia, conjunctivitis, endocarditis and endophthalmitis (2,3). Nasopharyngeal carriage is present in approximately 10% of healthy individuals, and these carriers have the main role in the spread of the agent since they do not show any signs of disease. Transmission occurs by contact with secretions or droplets (4).

Risk groups include those living in crowded living conditions, military personnel, students, those living in endemic areas in terms of meningococcus, those exposed to smoking, sickle cell patients and those with immunodeficiency.

The disease process can progress rapidly. Important non-specific findings include high fever, restlessness in the infant period, headache, nausea, vomiting and nuchal rigidity. Meningococcemia occurs in approximately half of the cases, and petechiae and purpura are not always observed (5-7). Meningococcemia is a sudden-onset, acute and rapidly progressing disease characterized by bacteremia and sepsis, high fever, and petechiae on the skin, with a high mortality rate that may lead to septic shock and multi-organ failure (8). Despite all treatment options, 10-15% of cases end in death and 10-20% of cases progress with severe morbidities such as hearing loss and limb amputations (9).

Meningitis occurs when the agent taken by direct contact or droplet into the respiratory secretions of the carrier or patient adheres to the mucosa of the nasopharynx, is carried to the deeper tissues by phagocytic vacuoles in the membrane, reaches the submucosa, invades the vessels in this area, and joins the circulation, and then reaches the meninges within hours (10). The diagnosis is made by microscopic observation of meningococci and isolation of the agent by culture from samples obtained from sterile body fluids such as synovial fluid, blood, and cerebrospinal fluid (CSF). CSF culture is the gold standard for diagnosis. polymerase chain reaction is important for the rapid diagnosis of meningococcal infections (11,12).

Early diagnosis is very important for the successful treatment of meningococcal infection and antibiotherapy constitutes the most important step. Therefore, empirical antibiotic treatment should be initiated without waiting for the culture results (13). Beta lactams should be the first antibiotic group preferred in treatment. Alternatively, cefotaxime, ceftriaxone, or benzathine penicillin G should be started and the duration of antibiotherapy should not be less than 7 days (13,14). In meningococcal disease, the risk of infection in close contacts is increased by 500 to 800 times (15). The decision to give prophylaxis should be based on the closeness and duration of contact. Prophylaxis should be given to people who share the same house, those who stay in collective living areas, and those who come into contact with the sick person or respiratory secretions up to 7 days before the onset of symptoms (16).

Vaccination is very important in the prevention of meningococcal infections and epidemics (17). Since meningococci that cause invasive meningococcal disease (IMD) are largely encapsulated, capsule polysaccharides have been targeted in vaccine development studies (18). According to polysaccharide capsule structure, 13 serotypes have been defined, and 6 of them (A, B, C, W135, X, Y) cause IMD meningococcal vaccines are of two types based on their development technique, and these are conjugated and polysaccharide vaccines (19).

Our study aims to organize a training program increase the level of knowledge about non-EPI vaccines in the residency program, and to emphasize the issue of meningococcal disease and newly developed meningococcal vaccines, which have high mortality and morbidity and can be prevented with vaccination. Evaluation of knowledge will be made before and after the training.

MATERIALS and METHODS

Study Type

Our descriptive cross-sectional study was conducted from 1 February to 31 March 2023 in University of Health Sciences

Türkiye, Adana City Training and Research Hospital, prior to the commencement of the study, written permissions were obtained from the administrations of the universities whose students were to be included in the study's sample. The approval of the University of Health Sciences Türkiye, Adana City Training and Research Hospital Clinical Research Ethics Committee and was obtained (decision number: 2360, date: 01.02.2023).

Study Group

The research population consisted of 125 family medicine residents working in the ACTR Hospital. In the calculation made with the Epi-Info statistical program, the sample size was found to be 102 people with 80% power, 95% confidence interval, and 5% margin of error. Residents who agreed to participate and completed the consent form were included in the study, while those who did not agree or who later withdrew consent were excluded.

Procedures

Before the training date, the participants were asked about sociodemographic data, knowledge, and attitudes about meningococcal infection and vaccines through both face-to-face interviews and an online questionnaire designed by the researcher.

Afterwards, a presentation titled "meningococcal infections and prevention" was made by a specialist physician through face-to-face and simultaneous video interviews in the family medicine clinic.

The content of the presentation consisted of epidemiology, prevalence, incidence, clinical features, licensed vaccines, and administration schemes according to age. After the presentation, the same questionnaire was re-administered to the participants who had taken the pretest and attended the presentation.

Structured questionnaire-data form used in our study consisted of sociodemographic data and questions created by the researcher. Cronbach's alpha value was found to be 0.75, and the questionnaire was considered valid and reliable. In the first part of the data collection form, 13 questions defined the demographic characteristics of the physicians. The questions about sociodemographic characteristics included the participant's age, gender, marital status, having children, total working time in the profession, the number of years in residency, whether the participant had a pediatric rotation, and whether the participant had ever encountered meningococcal infection. whether the physician has sufficient knowledge about meningococcal vaccines, whether he/she would have his/her own child vaccinated with the meningococcal vaccine, whether he/she wants the meningococcal vaccine to be included in the national vaccination calendar, and whether he/she recommends families to have their children vaccinated with the meningococcal vaccine. In the section assessing physician knowledge, there are twenty-six questions evaluating the level of knowledge about meningococcal infection and vaccination. The response options "Agree", "Disagree", and "No Opinion" were used.

Statistical Analysis

The data were analyzed with SPSS 21.0 at a 95% confidence level. The kurtosis and skewness coefficients were examined to determine the suitability of the variables to follow a normal distribution. Pre-post test change in Knowledge Level of Meningococcal Infection and Vaccines was analyzed with the dependent groups t-test. Pre-post test scores of Meningococcal Infection and Vaccines Knowledge Level were analyzed with independent groups t-test for variables with 2 groups and an ANOVA test for variables with 3 or more groups. P-value <0.05 was considered statistically significant.

RESULTS

A total of 102 people participated in the study. Among the participants, 56.9% were women, 49.0% were 30 years of age or younger, 57.8% were married, 37.3% had children, 34.3% had been practicing medicine for 1-3 years, 68.6% were full-time residents, 27.5% were in their first year of residency, and 71.6% had received pediatric rotation (Table 1). The percentage of residents who had experienced a patient with meningococcal infection during their careers was 31.4%. The percentage of residents who had sufficient knowledge about the meningococcal vaccine was 29.4%. The percentage of residents who stated that they would have their child vaccinated with the meningococcal vaccine was 89.2%. The percentage of residents who thought that the meningococcal vaccine should be included in the national vaccination schedule was 95.1%. Finally, the percentage of residents who recommended that families have their children vaccinated with the meningococcal vaccine was 94.1% (Table 1).

Most correct answers for the Pre-test: people in close contact with invasive meningococcal infection should receive antibiotic prophylaxis within the first 24 hours (93.1%); meningococcal vaccines are included in the routine vaccination schedule in our country (91.2%); *neisseria meningitidis* is transmitted by droplet or close contact through the nose or throat (90.2%); individuals with functional/anatomical asplenia and complement C5-C9 deficiency have an increased risk of meningococcal disease (90.2%); thirteen serotypes of meningococci have been identified, five of which (A, B, C, W135 and Y) cause the most disease (83.3%). The least correct answers for the Pre-test are: Trumenba (MenB-FHbp) and Menquadfi (MenACWY-TT) vaccines were licensed in our country in 2022 (13.7%). The only vaccine licensed for serogroup B in Türkiye is Trumenba (MenB-FHbp) (31.4%). Conjugated vaccines are not used in children under two years of age due to the weak immune response they induce (34.3%). Menveo (MenACWY-CRM) vaccine is used in children (from the 2nd month), adolescents, and adults (37.3%) Table 2. Polysaccharide meningococcal vaccines provide lifelong protection (40.2%).

Table 1. Pre-Post Test Intragroup and Intergroup Investigation of Knowledge Level of Meningococcal Infection and Vaccines

		Pre-educ		Post-educ		Mean average	t	p-value
		Mean±SD						
Age	<30	14.68±4.93		22.34±2.4		7.66	-12.801	0.000*
	30-34	17±3.37		23.25±1.81		6.25	-9.685	0.000*
	⩾35	18.75±3.07		23.19±1.22		4.44	-5.577	0.000*
		F=6.922	p=0.002*	F=2.398	p=0.096			
Gender	Male	16.61±3.77		22.93±1.96		6.32	-10.512	0.000*
	Female	15.78±4.86		22.69±2.19		6.91	-12.593	0.000*
		t=0.947	p=0.346	t=0.579	p=0.564			
Marital status	Single	15.05±4.67		22.67±1.8		7.63	-12.03	0.000*
	Married	16.93±4.09		22.88±2.28		5.95	-11.647	0.000*
		t=-2.166	p=0.033*	t=-0.493	p=0.623			
Medical experience	<3	14.09±4.97		21.8±2.47		7.71	-10.196	0.000*
	4-7	16.59±3.92		23.33±1.78		6.74	-11.373	0.000*
	⩾8	18.57±2.84		23.29±1.35		4.71	-7.584	0.000*
		F=8.217	p=0.000*	F=6.756	p=0.002*			
Residency type	Full-time	15.37±4.65		22.59±2.17		7.21	-14.943	0.000*
	Half-time	17.81±3.35		23.25±1.83		5.44	-7.706	0.000*
		t=-2.665	p=0.009*	t=-1.503	p=0.136			
Experience of patients with meningococcal infection	Yes	17.41±3.88		22.97±1.99		5.56	-8.654	0.000*
	No	15.56±4.55		22.71±2.13		7.16	-14.222	0.000*
		t=1.988	p=.049*	t=0.570	p=0.570			
Thinking that they have sufficient knowledge about meningococcal vaccine	Yes	18.63±3.08		23.3±1.82		4.67	-7.393	0.000*
	No	15.1±4.49		22.58±2.16		7.49	-15.621	0.000*
		t=4.578	p=0.000*	t=1.594	p=0.114			
Thinking that meningococcal vaccine should be included in the national vaccination schedule	Yes	16.05±4.5		22.76±2.12		6.71	-15.829	0.000*
	No	17.8±1.79		23.4±1.14		5.60	-8.257	0.001*
		t=-0.861	p=0.391	t=-0.665	p=0.508			
Recommending meningococcal vaccination to families	Yes	16.26±4.39		22.8±2.12		6.54	-15.798	0.000*
	No	14.17±4.79		22.67±1.63		8.50	-4.576	0.006*
		t=1.127	p=0.262	t=0.154	p=0.878			

*p<0.05 Paired Sample t test, independent Sample t test, ANOVA, SD: Standard deviation

Table 2. Questions with the highest increase in correct answers	
Trumenba (MenB-FHbp) and Menquadfi (MenACWY-TT) vaccines were licensed in our country in 2022	▲49%
The only vaccine licensed for serogroup B in Türkiye is Trumenba (MenB-FHbp)	▲43%
Menveo (MenACWY-CRM) vaccine is used in children (from the 2nd month), adolescents and adults	▲42%
Menectra (MenACWY-DT) vaccine can be used between the ages of 9 months and 55 years. The vaccine is used in single doses in people older than two years of age.	▲41%
The source of meningococcal infections is mostly asymptomatic infectious carriage	▲41%

Most correct answers for the final test; with the introduction of conjugated pneumococcal and Hib vaccines into routine vaccination schedules world-wide, *neisseria meningitidis* is now the leading cause of meningitis, accounting for 99.0% of cases. People in close contact with invasive meningococcal infection should receive antibiotic prophylaxis within the first 24 hours. Individuals with functional/anatomical asplenia and complement C5-C9 deficiency have an increased risk of meningococcal disease, meningococcal vaccines are included in the routine vaccination schedule in our country, *neisseria meningitidis* is transmitted through close contact or droplets from the nose or throat, accounting for 97.1% of transmissions. The least correct answers in the post-test; trumenba (MenB-FHbp) and Menquadfi (MenACWY-TT) vaccines were licensed in our country in 2022, polysaccharide meningococcal vaccines provide substantial protection, with an efficacy of 69.6%, over a lifetime, conjugated vaccines are not used in children under two years of age due to the weak immune response they induce. The only vaccine licensed for serogroup B in Türkiye is Trumenba (MenB-FHbp), which has an effectiveness of 74.5%, meningococcal infection is more common in children under 2 years of age in developing countries, and over 10 years of age in developed countries.

DISCUSSION

The rate of those who had experienced a patient with meningococcal infection during their professional life was 31.4% in our study, and this rate was 51.9% in a study conducted by Kapar (20) with pediatric specialists and assistants. In a study conducted by Aycanoğlu (21) with 193 physicians-120 family physicians, 39 family medicine residents, and 34 family medicine physicians-it was found that 32.1% of the participants had experience with meningococcal infection. Since meningitis infections usually have an acute onset, rapidly and noisily progressing clinical picture; the first presentation is mostly to secondary and tertiary healthcare institutions rather than primary care, and therefore pediatricians are more likely to encounter these cases than family physicians. The result of our study confirms this situation.

In our study, the rate of those who thought they had sufficient knowledge about meningococcal vaccine was 29.4% before the training and 80.3% after the training; in Kolcu (22), in which a total of 236 physicians (143 family GPs, 70 family medicine residents, 20 family medicine specialists) participated, the rate of participants who considered themselves sufficiently knowledgeable about meningococcal vaccines was 12.7%. In a study conducted by Avcı (23) with 377 family physicians on vaccines other than the national vaccination schedule, 26% of the participants considered themselves knowledgeable about special vaccines, while 56.5% stated that they had partial knowledge. In the same study, 88.7% of those who thought they did not have sufficient knowledge about special vaccines suggested in-service training as a method of obtaining information.

The rate of those who thought that meningococcal vaccine should be included in the national vaccination schedule was 95.1% in our study. In Avcı (23), 69.4% of the participants stated a positive opinion. In Kolcu (22), 70.4% of the participants answered yes to the same question, while 26.9% were undecided. In the study conducted by Özdemir et al. (24) with pediatricians, this rate was 81.8%. Participants who responded negatively cited the high cost of vaccination (56.6%), the idea that it was not a priority (42.3%), side effects (15.4%), and not finding it effective (7.7%) as reasons. In the Aycanoğlu (21), 82.9% of the participants selected the option "I think that meningitis vaccine should be included in the routine vaccination schedule due to the high mortality and morbidity rates of meningococcal meningitis." The rate of those who think that meningococcal vaccines should be included in the national calendar was found to be higher than in other studies.

The correct response rate to the statement that there are two types of meningococcal vaccines, polysaccharide and conjugated, was 77.5% in the Pre-test and 87.3% in the post-test in our study. 61.53% of the participants in Kapar (20) stated that there are two types of vaccines. In the Özdemir et al. (24) study conducted with pediatricians, 87.6% of the participants answered the same question correctly, and in the Avcı (23) study, 72.9% of the participants answered the same question correctly. The correct response rate to another statement that meningococcal vaccines have vaccine forms containing a single serotype and vaccine forms containing multiple serotypes was 71.6% in the Pre-test and 95.1% in the post-test in our study, while the correct response rate for the same statement was 68.9% in Aycanoğlu (21) Again, while the correct response rate of the false statement "polysaccharide meningococcal vaccines provide permanent immunity" was 40.2%, 35.8% of the participants in Aycanoğlu (21) chose the option of disagreeing with the statement

"polysaccharide meningococcal vaccines provide lifelong protection." In general, it was observed that participants' knowledge of meningococcal infection was higher than that of meningococcal vaccines. This shows that more emphasis should be placed on vaccination in the training sessions to be organized.

The Meningococcal Infection and Vaccines Knowledge Level Pretest score shows a statistically significant difference according to age ($p<0.05$). Those under 30 years of age have a mean score of 14.68; those between 30-34 years of age have a mean score of 17.00; and those 35 years of age and older have a mean score of 18.75. Accordingly, the average income of those aged 35 years and over is the highest. Again, Meningococcal Infection and Vaccines Knowledge Level Pretest score shows a statistically significant difference based on the length of practice ($p<0.05$).

The mean of those who have been practicing for 1-3 years is 14.09; the mean of those who have been practicing for 4-7 years is 16.59; and the mean of those who have been practicing for 8 years or more is 18.57. Accordingly, the average of those who have been practicing for 8 years or more is the highest. Similarly, the post-test score of Knowledge Level of Meningococcal Infection and Vaccines showed a statistically significant difference according to the duration of practice ($p<0.05$). The mean score is 21.80 for those who have been practicing for 1-3 years; 23.33 for those who have been practicing for 4-7 years; and 23.29 for those who have been practicing for 8 years or more. Accordingly, the average of those who have been practicing for 4-7 years is the highest.

In Aycanoğlu (21), it was observed that the level of knowledge of meningococcal infection was higher in employees working for 20 years or more compared to the others. It may be thought that age and years spent in the profession, and thus experience, may have led to this result. Primary care/family medicine forms the basis of preventive medicine practices. Vaccination studies are one of the most important parts of the research. In addition, family medicine involves managing conditions with low prevalence. Therefore, always being prepared is required for any disease, no matter how rare it is in the community. Meningococcal vaccines are not yet included in the national vaccination schedule in Türkiye. Therefore, physicians do not have as much practice with meningococcal vaccines as with other vaccines on the schedule. This causes the information acquired over time to be forgotten or not kept up to date. As a matter of fact, most of the physicians who answered "no" to the question posed by Kolcu (22) about recommending that families have their children vaccinated with the meningococcal vaccine claimed that they did not have sufficient knowledge to provide education about the vaccine.

Study Limitation

This study was conducted in a single center as a survey. With a multicenter design, it is possible to define the state of knowledge about Meningococcal Infection and Vaccines in Family Medicine education both in other centers and nationally in a more inclusive manner. The strength of our study is that it was conducted among family medicine residents who will actively assume immunization responsibility in primary care. In addition, the provision of opportunistic education was provided indirectly and the simultaneous assessment of knowledge and attitudes regarding infections, clinical practices, and vaccines is one of the strengths of our study.

CONCLUSION

Family physicians serve individuals seeking medical care irrespective of age, gender and disease. Vaccination is undoubtedly a fundamental task for family physicians. Meningococcal disease, a vaccine-preventable disease with high mortality and morbidity despite treatment, can be considered critical in this respect.

The data obtained in our study showed that family physicians may be hesitant about non-EPI vaccines and that they are more knowledgeable about the disease related to these vaccines than about meningococcal vaccination. Awareness and knowledge increased after the education program. Preventive medicine, involving physicians who will be more motivated towards taking measures before individuals get sick, will prevent congestion in the health system in the future. In addition, the feedback mechanism will provide guidance for future education programs. This will also provide reference information for family medicine trainers.

Ethics

Ethics Committee Approval: The approval of the University of Health Sciences Türkiye, Adana City Training and Research Hospital Clinical Research Ethics Committee and was obtained (decision number: 2360, date: 01.02.2023).

Informed Consent: Residents who agreed to participate and completed the consent form were included in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.T., H.V.T., Concept: A.T., M.T., H.V.T., Data Collection or Processing: A.T., H.V.T., Analysis or Interpretation: A.T., M.T., H.V.T., Literature Search: A.T., M.T., Writing: A.T., M.T., H.V.T.

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Original Article

Evaluation of the Relationship Between the Causative Microorganism and Procalcitonin Levels in Intensive Care Patients

Yoğun Bakım Hastalarında Etken Mikroorganizma ile Prokalsitonin Düzeyleri Arasındaki İlişkinin Değerlendirilmesi

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ABSTRACT

Objective: In intensive care units, various inflammatory and immunological markers, along with the patient's clinic, are used to select the appropriate empirical antibiotic therapy until blood culture results are obtained. Of these markers, C-reactive protein (CRP) and procalcitonin (PCT) are frequently used. Our study aimed to evaluate the relationship between microorganism grown in blood culture and PCT level.

Material and Methods: In our study, following the approval of the ethics committee, the demographic data, blood culture growths, and CRP and PCT values of the patients who were followed up with a diagnosis of bloodstream infection in the intensive care unit for a six-month period between 15.11.2022 and 15.05.2023 were recorded retrospectively. Repetitive culture growths and contaminated cultures were excluded from the study.

Results: The total number of cultures included in the analysis was 510, of which 172 were Gram-negative, 304 were Gram-positive, and 34 were for fungal infection. When Gram-negative cultures were examined, the most common agents were *Escherichia coli* (29.0%) and *Klebsiella pneumoniae* (27.9%), respectively. When we looked at Gram-positive cultures, *Staphylococcus hemoliticus* (24.7%), *Staphylococcus hominis* (18.8%) and *Staphylococcus auerus* (14.4%) were the most common factors, respectively. All fungal cultures consisted of *Candida species*. When the PCT levels of the groups were examined, it was seen that the values were statistically significantly higher in the Gram-negative bacteria group ($p<0.001$). In comparisons between groups, CRP levels were found to be statistically higher in the Gram-negative group than in both the Gram-positive and fungal groups ($p<0.001$, $p<0.001$, respectively).

Conclusion: We think that looking at serum PCT levels will guide us in estimating the agent in choosing the empirical antibiotic therapy that should be started until the culture agent is identified.

Keywords: Procalcitonin, bacteremia, C-reactive protein, Gram-negative

ÖZ

Amaç: Yoğun bakımlarda kan kültürü üremeleri sonuçlanana kadar geçen zamanda uygun ampirik antibiyoterapinin seçimine yönelik hastanın kliniği ile birlikte çeşitli enflamatuvar ve immünolojik belirteçlerden faydalanılmaktadır. Bunlar arasında C-reaktif protein (CRP) ve prokalsitonin (PCT) sıkça kullanılmaktadır. Çalışmamızda kan kültüründe üreyen etkenler ile PCT arasındaki ilişkinin değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Çalışmamızda etik kurul onayını takiben 15.11.2022- 15.05.2023 tarihleri arasında altı aylık dönemde yoğun bakımda kan dolaşım enfeksiyonu tanısı ile takip edilmiş hastaların demografik verileri, kan kültürü üremeleri, kültür alımından 24. saat öncesine ait CRP ve PCT değerleri retrospektif olarak kaydedildi. Tekrarlayan kültür üremeleri ve kontamine kültürler çalışma dışı bırakıldı.

Bulgular: Analize dahil edilen toplam kültür sayısı 510 olup, bunların 172'si Gram-negatif, 304'ü Gram-pozitif ve 34'ü mantar enfeksiyonu idi. Gram-negatif etkenler incelendiğinde en sık etken sırasıyla *Escherichia coli* (%29,0) ve *Klebsiella pneumoniae* (%27,9) idi. Gram-pozitif kültürlere baktığımızda ise sırasıyla *Staphylococcus hemoliticus* (%24,7), *Staphylococcus hominis* (%18,8) ve *Staphylococcus auerus* (%14,4) en

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ÖZ

sık görülen etkenlerdi. Mantar kültürlerinin tamamı *Candida* türlerinden oluşmaktaydı. Grupların PCT düzeyleri incelendiğinde Gram-negatif bakteri grubunda değerlerin istatistiksel olarak anlamlı derecede yüksek olduğu görüldü (p<0,001). Gruplar arası karşılaştırmalarda CRP düzeylerinin Gram-negatif grubunda hem Gram-pozitif hem de mantar gruplarına göre istatistiksel olarak anlamlı derecede yüksek olduğu görüldü (sırasıyla p<0,001, p<0,001).

Sonuç: Bakteriyemi etkenini tahmin edilip kültür etkeni ortaya konuluncaya kadar başlanması gereken ampirik antibiyoterapinin seçiminde serum PCT değerlerine bakılmasının bize yol gösterici olacağı düşüncesindeyiz.

Anahtar Kelimeler: Prokalsitonin, bakteriyemi, C-reaktif protein, Gram-negatif

INTRODUCTION

Although bloodstream infections are common in patients followed in intensive care units, they are associated with high mortality (1). Early diagnosis and targeted empirical treatment are of high prognostic importance (2). Delay in initiating adequate antibiotic therapy is an independent indicator of high mortality. Various inflammatory and immunological markers are used, together with the patient's clinical information, for the selection of the appropriate empirical antibiotic therapy until the blood culture results are completed. Among these, C-reactive protein (CRP) and procalcitonin (PCT) are frequently used (3,4). Because PCT rises earlier in serum and has higher sensitivity and specificity than CRP against systemic bacterial infections, it guides us in the treatment and follow-up of bloodstream infections (2). In addition, high PCT concentrations have a positive predictive value for severe sepsis and septic shock, and distinguish between viral and bacterial infections (5). However, there are recent studies showing that PCT can also help predict the causative microorganism (6,7). In these studies, it is stated that the PCT level can be used to differentiate bacteremia caused by Gram-positive and Gram-negative bacteria, but more studies are needed on this subject. In our study, we aimed to evaluate the relationship between CRP and PCT levels according to the causative microorganism in the blood culture.

MATERIALS and METHODS

Ethical approval was obtained for the study from the Eskişehir Trainig and Research Hospital of Medicine Non-interventional Clinical Research Ethics Committee (decision number: ESH/GOEK2023/29, date: 20.06.2023). All procedures were performed according to the ethical rules and principles of the Declaration of Helsinki.

Study Population

In our study, patients who were followed up with the diagnosis of bloodstream infection in the intensive care unit for a six-month period between 15.11.2022 and 15.05.2023, demographic data, blood culture reproductions, CRP and PCT values 24th hours before culture were retrospectively recorded after following the approval of the ethics committee. The causative microorganisms were separated according to their Gram stain properties; examined in three groups, and their CRP and PCT values were compared.

Pathogenic microorganism growths in blood cultures not associated with another focus were included in the study, according to laboratory-confirmed bloodstream infection criteria defined in the Centers for Disease Control and Prevention guideline for patients over the age of 18 who were followed in intensive care units (8). Multiple blood cultures from the same patients, blood cultures suspected of contamination, and blood culture results from patients under 18 years of age were excluded from the study. Blood culture samples were studied with BD Bactec automated blood culture systems. The remaining blood culture growths were examined by dividing them groups: group 1, Gram-negative bacteria; group 2, Gram-positive bacteria; group 3, fungal organisms.

Statistical Analysis

The normality of the distributions of continuous variables was checked with the Shapiro–Wilk test, and the homogeneity of group variances was checked with the Levene test. Descriptive statistics for continuous variables with a non-normal distribution are expressed as the median (lowest-highest value), while categorical variables are expressed as the number of cases and percentage (%). In group comparisons, normally distributed data were compared with the t-test, and non-normally distributed data were compared with the Mann-Whitney U test. Logistic regression analysis was used to evaluate differences in PCT levels between groups. Statistical significance was set at p<0.05. All statistical analyses were performed using SPSS 22.0 (IBM SPSS Ver. 22.0, IBM Corp, Armonk, NY, USA).

RESULTS

The total number of cultures included in the analysis was 510, and 172 cultures were Gram-negative, 304 cultures were Gram-positive, and 34 cultures constituted the fungal infection group. When Gram-negative agents are examined, the most common agents are *Escherichia coli* (29.0%) and *Klebsiella pneumoniae* (27.9%). When we look at Gram-positive agents, *Staphylococcus haemolyticus* (24.7%), *Staphylococcus hominis* (18.8%), and *Staphylococcus aureus* (14.4%) were the most common ones, respectively. All of the fungal agents were *Candida species* (Table 1). There was no significant difference

between the groups in terms of age and gender. When the CRP and PCT levels among the groups were examined, it was found that these levels were statistically significant and higher in the Gram-negative bacteria group (CRP: p<0.001, PCT: p<0.001). In the comparison of CRP and PCT values between the groups, CRP and PCT values were found to be significantly higher in the Gram-negative group than in the Gram-positive group (p<0.001, p<0.001, respectively) (Table 2). It was also observed that the Gram-negative group was significantly higher than the fungal infection group with respect to CRP (p<0.001) (Table 3).

DISCUSSION

In our study, we showed that CRP and PCT levels were higher in the Gram-negative bacteria group than in the other groups. This is one of the pioneering studies showing that acute phase reactants can give clues not only about the severity of the infection but also about the causative agent.

Bloodstream infections are frequently seen and are serious causes of mortality and morbidity in intensive care; however, the factors vary in every region and even in every hospital. In studies conducted in Türkiye, it was stated that Gram-positive agents were the most common in intensive care units, while *Staphylococci* were the most common agents among them. The Gram-negative bacteria group was emphasized as the second most common, with *Acinetobacters* being the most common (9,10). In our study, in parallel with the literature, Gram-positive bacteria were mostly encountered in the intensive care unit, and *Staphylococc*i constituted the majority of them. When Gram-negative agents are considered, the most common agents in our hospital were *Escherichia coli* and *Klebsiella pneumoniae*.

Early diagnosis of bloodstream infections and initiation of an appropriate empirical antibiotic therapy significantly reduce mortality in studies conducted in intensive care units. Initiation of an inappropriate antimicrobial therapy at baseline, was found to be an independent risk factor for adverse outcomes in patients with bloodstream infections of *Staphylococcus aureus* and Gram-negative origin (11,12). Studies have emphasized that an inappropriate initial antimicrobial therapy is strongly associated with adverse outcomes in bloodstream infections caused by antibiotic-resistant nonfermenting Gram-negatives such as *Pseudomonas aeruginosa* (13). Therefore, the estimation of causative microorganisms is important for clinicians. In our study, the differences in serum PCT levels between the different agents were examined, and these levels were found

Table 1. Distribution of culture according to species

Group 1 Gram-negative bacteria (n=172)	Group 2 Gram-positive bacteria (n=304)	Group 3 Fungal group (n=34)
Escherichia coli (n=50) 29.0%	*Staphylococcus* hemolyticus (n=75) 24.7%	*Candida species* (n=34) 100%
Klebsiell pneumoniae (n=48) 27.9%	*Staphylococcus* hominis (n=57) 18.8%	
Acinetobacter baumanii (n=37) 21.5%	*Staphylococcus* aureus (n=44) 14.4%	
Pseudomonas aureginosa (n=14) 8.1%	The other *Staphylococcus. spp* (n=47) 15.4%	
Proteus mirabilis (n=7) 4.0%	*Enterococcus faecium* (n=28) 9.2%	
The other *spp.* (n=16) 9.5%	*Enterococcus faecalis* (n=27) 8.8%	
	Streptococcus spp. (n=16) 5.2%	
	The other *spp.* (n=10) 3.5%	

Table 2. Change of demographic data and acute phase reactants between groups

	Group 1 (n=172)	Group 2 (n=304)	Group 3 (n=35)	p value
Age	73 (62-82)	74 (66-82)	70 (60-79)	0.097
Gender (male, n)	87	150	16	0.868
Procalcitonin (ng/mL)	5.24 (1.06-16.09)	0.52 (0.14-2.57)	0.59 (0.36-3.14)	<0.001
CRP (ng/mL)	152 (75-218)	96 (49.5-160.5)	112 (75-178.5)	<0.001
CRP: C-reactive protein				

Table 3. Significance values of CRP, PCT values between groups

	CRP level	Procalcitonin level
Group 1 vs group 2	<0.001	<0.001
Group 1 vs group 3	<0.001	0.103
Group 2 vs group 3	0.288	0.119
CRP: C-reactive protein, PCT: Procalcitonin		

to be statistically significant in the Gram-negative bacteria group.

In recent studies, it has been emphasized that the PCT response is different in Gram-negative and Gram-positive bacteria (6,7). PCT expression is induced by the stimulation of various inflammatory *Cytokines,* and it is thought that the main reason for this difference is the activation of different pathways by bacteria (14,15). *Lipopolysaccharides* in Gram-negative bacteria stimulate Toll-like receptor-4, while lipoteichoic acid in Gram-positive bacterial cell walls stimulates Toll-like receptor-2 (16). This leads to differential production of inflammatory *Cytokines* in the respective *Leukocytes* (17). This concept suggests that different pathogens may lead to different levels of PCT production (18-20). Thomas et al. (14) found higher levels of IL-6 and IL-8 in Gram-negative bacterial infections, which further increased the accuracy of the variable response. The mechanisms of lower production of PCT by Gram-positive agents, have not been fully elucidated, and attempts have been made to explain different mechanisms of action regarding the immune response, such as the inhibitory effect of *Enterococci* on macrophage activation, antibodies activated by *Staphylococcus aureus*, and the innate immune response triggering effect of T-lymphocytes (21,22). In our study, in parallel with the literature, Gram-negative bacterial infections induced more severe PCT and CRP responses.

Martini et al. (23) found that a PCT limit of 2.0 ng/mL was able to differentiate between *Candida species* and bacterial sepsis in 48 intensive care patients with signs of sepsis at high risk for fungal infection. In contrast, Fu et al. (24) found a cut-off value of 8.06 ng/mL in the distinction between candidemia and Gram-negative bacterial sepsis in their study of 85 patients. Since PCT values can differ significantly in different clinical diseases and especially in intensive care patients, they said that making this inference depends on the clinical characteristics of the patient population studied, and furthermore, they predicted that a definite conclusion could not be reached. In our study, the PCT level was found to be high (especially in the Gram-negative bacteria group), but the patients were not separated according to their clinical characteristics (5.24 vs. 0.52, $p<0.001$).

The most important limitations of the study, including its retrospective type and the lack of homogeneity in numbers among the groups, can be listed as follows. The Gram-positive infection group is almost twice that of the Gram-positive group. In addition, the number of fungal groups is very small.

Study Limitation

Considering the limitations of the study, its retrospective type and the lack of homogeneity in numbers among the groups can be listed as the most important ones. The Gram-positive infection group is almost twice as high as the Gram-negative group. In addition, the number of fungal group is very small.

CONCLUSION

PCT levels were found to be higher in Gram-negative agents than in Gram-positive agents. We think that looking at serum PCT values will guide us in the selection of empirical antibiotherapy, which should be initiated while the bacteremia agent is being identified and the culture results are pending.

Ethics

Ethics Committee Approval: Ethical approval was obtained for the study from the Eskişehir Trainig and Research Hospital of Medicine Non-interventional Clinical Research Ethics Committee (decision number: ESH/GOEK2023/29, date: 20.06.2023).

Informed Consent: Informed consent was obtained from all participants.

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Footnotes

Author Contributions

Surgical and Medical Practices: A.A., A.D., Concept: A.A., A.D., Design: A.A., A.D., Data Collection or Processing: A.D., Analysis or Interpretation: A.D., Literature Search: A.A., A.D., Writing: A.A.

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Case Report

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Glucose-6-Phosphate Dehydrogenase Deficiency: Case Report

Glukoz-6-Fosfat Dehidrogenaz Eksikliği: Olgu Sunumu

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ABSTRACT

A Glucose-6-phosphate dehydrogenase (G6PD)-deficient patient, therefore, lacks the ability to protect red blood cells against oxidative stresses from certain drugs, metabolic conditions, infections, and ingestion of fava beans. Numerous drugs, infections, and metabolic conditions have been shown to cause acute hemolysis of red blood cells in the G6PD-deficient patient, with the rare need for blood transfusion. The most effective management strategy is to prevent hemolysis by avoiding oxidative stressors. This report presents a case of general anesthesia management in a patient with G6PD deficiency. A 28-year-old male with G6PD deficiency was scheduled for plastic surgery operation under general anesthesia with total intravenous anesthesia (TIVA) including propofol and remifentanyl. The intraoperative and postoperative course was uneventful with respect to hemolytic problems, malignant hyperthermia or methemoglobinemia. We think that general anesthesia with TIVA can be performed successfully with special attention in patients with G6PD deficiency.

Keywords: Glucose-6-phosphate dehydrogenase deficiency, TIVA, general anesthesia

ÖZ

Glukoz-6-fosfat dehidrojen (G6PD) eksikliği olan hastalarda belirli ilaçların, metabolik durumların, enfeksiyonların ve bakla bitkisinin sindiriminin yol açtığı oksidatif strese karşı eritrositleri koruma yeteneği eksiktir. G6PD eksikliği olan hastalarda pek çok ilacın, enfeksiyonların ve metabolik durumların kırmızı kan hücrelerinde, nadiren kan transfüzyonu gerektiren, akut hemolize yol açtığı bilinmektedir. Hemolizi önlemede en etkin yönetim stratejisi oksidatif stresörlerden kaçınmaktır. Bu yazıda, G6PD enzim eksikliği olan bir hastadaki genel anestezi uygulaması sunuldu. Yirmi sekiz yaşındaki erkek hastaya plastik cerrahi operasyonu için propofol ve remifentanil içeren total intravenöz anestezi (TİVA) ile genel anestezi uygulandı. Ameliyat ve ameliyat sonrası dönem sorunsuz seyretti. Hemolitik sorunlar, malign hipertermi veya methemoglobinemi görülmedi. G6PD enzim eksikliği olan olgularda, özel dikkat ile TİVA'nın güvenle uygulanabileceğini düşünmekteyiz.

Anahtar Kelimeler: Glukoz-6-fosfat dehidrogenaz eksikliği, TİVA, genel anestezi

INTRODUCTION

The case was a 28-year-old male patient, weighing 83 kilograms, with a soft tissue mass in the left pectoral region and was planned to be operated by the plastic surgery clinic for breast and adipose tissue excision. From his medical history, it was learned that glucose-6-phosphate dehydrogenase (G6PD) deficiency was diagnosed at the age of 10 years following the development of abdominal pain and icterus following the ingestion of fava beans.

CASE REPORT

Physical examination revealed normal findings

In the preoperative laboratory examination, G6PD enzyme level was measured quantitatively as 2.4 IU/g hemoglobin (Hb) (4.6-13.5 IU/g Hb). Hb was 15.4 g/dL, hematocrit 45.6%, total bilirubin 1.4 mg/dL, direct bilirubin 0.1 mg/dL, lactate dehydrogenase (LDH) 10^3 U/L, uric acid 5.2 mg/dL, erythrocyte 5.150/mm³, platelet 165.000/mm³, international normalized ratio 1.26 mm³. No erythrocytes, Hb, bilirubin and urobilinogen were detected in the urine. Electrolyte and renal function test values were within normal limits.

After routine preparation, the patient was premedicated with 2.5 mg midazolam i.v. after 2 mg/kg propofol induction, the patient was intubated with 0.6 mg/kg rocuronium. Anesthesia maintenance was performed with 60% N_2O + 40% O_2, 10-15 mcg/kg/h remifentanil + 2-3 mg/kg/h propofol dose range with total intravenous anesthesia (TIVA). No additional muscle relaxant was administered to the patient throughout the operation. After 70 minutes of operation, a mixture of 2.5 mg neostigmine + 1 mg atropine sulfate was given to eliminate residual neuromuscular blockade. Morphine 1 mg/kg intravenously was administered intraoperatively for postoperative analgesia. The patient was hemodynamically

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stable in perioperative and postoperative follow-up, no respiratory problems and no adverse reactions to the drugs used were observed. The patient was discharged on the 3rd postoperative day without any problem in the ward follow-up.

DISCUSSION

G6PD deficiency is the most common enzymatic and X-linked disorder of red blood cells in humans. It is estimated that about 400 million people are affected by this deficiency (1). The highest prevalence of G6PD deficiency is reported in Africa, Southern Europe, the Middle East, South East Asia, and the central and Southern Pacific islands; however, because of migration, it is becoming more common all over the word (2). The G6PD enzyme catalyzes the first step in the pentose phosphate pathway, leading to antioxidants that protect cells against oxidative damage (3,4). The enzyme G6PD catalyzes the first step of the pentose phosphate pathway (Figure 1). The pentose phosphate pathway enables the formation of ribose-5-phosphate, a precursor of RNA, DNA, Adenosine Triphosphate, Coenzyme A, Nicotinamide Adenine Dinucleotide and Flavin Adenine Dinucleotide, from glucose and mediates the formation of Nicotinamide Adenine Dinucleotide Phosphate (NADPH). NADPH enables the reduction of glutathione in the cell. Reduced glutathione functions as an antioxidant and protects the cell against oxidative damage (5). In many cells, NADPH is also produced via other metabolic pathways, whereas in red blood cells there are no other metabolic pathways that produce NADPH, so G6PD enzyme deficiency results in a lethal state where any oxidative stress, especially in red blood cells, leads to hemolytic anemia. Some metabolic conditions such as ingestion of fava beans, certain drugs, infections and diabetic ketoacidosis can lead to oxidative stress (6). Acute intravascular hemolysis occurs 2-3 days after exposure to oxidative stressors. Hemolysis can be diagnosed by the presence of symptoms such as fatigue, dyspnea, lumbar or substernal pain. The patient may have tachycardia, cyanosis, pallor, icterus, and dark brown urine color. Laboratory evaluation may reveal anemia due to hemolysis, reticulocytosis, decreased serum haptoglobulin, increased indirect bilirubin level and LDH. Heinz bodies (denatured Hb accumulation in red blood cells) and schizocytosis may be observed in peripheral smear. Urinalysis shows hemosiderin, urobilinogen and brown urine. Since G6PD is not an autoimmune condition, Coombs test is negative. G6PD enzyme level in red blood cells and Heinz body detection are specific tests. "The Beutler enzyme spot test" is the diagnostic test for G6PD deficiency (7,8).

Hemogram and routine biochemical tests including indirect bilirubin, uric acid and LDH were performed once a day for three days to show hemolytic episode in the postoperative period. Since no clinical findings of hemolytic anemia and no abnormal values were found in the laboratory tests for three days, no additional tests were performed. At the outpatient clinic visit on the 7th postoperative day, the patient's complete blood count and biochemical tests were evaluated as normal.

The World Health Organization has classified G6PD enzyme deficiency into five classes according to enzyme activity level and clinical findings;

Class I: Enzyme activity is 10% below normal and chronic hemolytic anemia is observed.

Class II: Severe enzyme deficiency is present and intermittent hemolytic anemia (secondary to drugs, infection and chemicals) is usually detected.

Class III: Moderate (10-60%) enzyme deficiency and intermittent hemolytic anemia.

Class IV: Enzyme deficiency and hemolysis are not present.

Class V: Enzyme activity is high. Class IV and V have no clinical significance (9).

Since the enzyme level in our patient was 2.4 IU/g Hb (4.6-13.5 IU/g Hb), the patient was considered to have a moderate enzyme deficiency.

Altikat et al. (10) conducted studies to show the effects of many drugs, chemicals and anesthetic agents on G6PD enzyme activity. In the study conducted by Altikat et al. (10), it was suggested that anesthetic agents such as halothane, isoflurane, ketamine, sevoflurane, prilocaine, diazem and midazolam were effective on G6PD enzyme activity and especially sevoflurane, isoflurane, diazem and midazolam had inhibitory effects; however, it was reported that more studies should be conducted on the subject. Another study by Büyükokuroğlu and Süleyman (11) showed that diazepam and midazolam had inhibitory effects on G6PD enzymatic

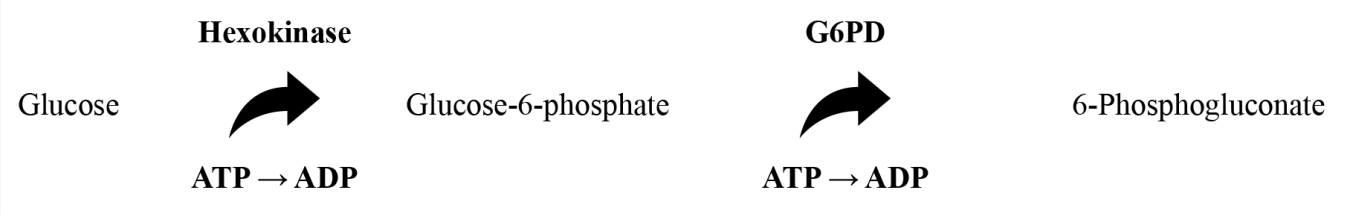

Figure 1. Hexose monophosphate shunt
G6PD: Glucose-6-phosphate dehydrogenase, ATP: Adenosine triphosphate, ADP: Adenosine diphosphate

Table 1. Drugs and chemicals causing hemolysis in G6PD deficiency		
Unsafe for classes I, II and III	**Safe for class II and III**	
Acetanilid	Acetaminophen	Pyrimethamine
Dapsone	Aminopyrine	Quinidine
Methylene blue	Ascorbic acid	Quinine
Nalidixic acid	Aspirin	Sulfamethoxypyridazine
Nitrofurantoin	Chloramphenicol	Streptomycin
Niridazole	Chloroquine	Sulfisoxazole
Primaquine	Colchicine	Trimethoprim
Toluidine blue	Diphenhydramine	Tripelennamine
Vitamin K	Isoniazid	Halothane
Sulfacetamide	L-DOPA	Prilocaine
Sulfamethoxazole	Menadione	Ketamine
Sulfanilamide	Paraminobenzoic acid	Fentanyl
Phenylhydrazine	Phenacetin	Propofol
Furazolidone	Phenytoin	Benzodiazepam (except diazepam)
Trinitrotoluene	Probenecid	
Toluidine blue	Procainamide	
G6PD: Glucose-6-phosphate dehydrogenase		

activity *in vitro* and increased the severity of hemolysis when used together with isofluorane and sevofluorane. Table 1 shows the list of safe and unsafe drugs resulting from these *in vitro* studies (6-12).

However, no cases have been reported showing that benzodiazepine, codeine/codeine derivatives, propofol, fentanyl or ketamine cause hemolytic crisis in vivo in patients with G6PD deficiency (13). However, studies on hemolytic crisis caused by inhalational anesthetic agents are still ongoing, especially some autonomists associate G6PD deficiency with malignant hyperthermia. In fact, there are not enough studies on the effects of inhalational anesthetic agents on patients with G6PD enzyme deficiency (13). These drugs interact with Hb and oxygen, leading to the intracellular formation of hydrogen peroxide and other oxidant radicals. These oxidant radicals accumulate in cells with enzyme deficiency, leading to oxidation of Hb and other proteins, thus leading to loss of function and cell death (6-14).

In our case, which was planned to be operated under general anesthesia, we preferred TIVA containing propofol and remifentanil as general anesthetic. We used midazolam for premedication, propofol for induction and rocuronium for intubation. We administered morphine as analgesic. We did not observe any side effects to any of the drugs.

In a study conducted by Ozmen et al. (14), the effects of analgesic agents such as remifentanil hydrochloride, fentanyl citrate, alfentanil hydrochloride and pethidine hydrochloride on G6PD activity were investigated. Although remifentanil hydrochloride and fentanyl citrate inhibited G6PD enzyme activity in healthy individuals, it was found that enzyme activity did not change in two of the three individuals with G6PD deficiency included in the study, and alfentanil hydrochloride and pethidine hydrochloride had no effect on enzyme activity in both healthy individuals and those with G6PD deficiency. In 2008, Wada et al. (15) reported that midazolam was safely used in induction in a 5-year-old patient diagnosed with G6PD deficiency who underwent laparoscopic cholecystectomy surgery in Japan. In a retrospective study published in 2013 by John et al. (16), all patients were given propofol, pancuronium or suxamethonium, neostigmine, atropine, and amoxicillin. Halothane was administered to 17 patients, isoflurane to 5 patients, fentanyl to 15 patients, pentazocine to 7 patients, midazolam to 4 patients, and diazepam to 18 patients, and no hemolysis was observed in any of the patients during the one-week follow-up period. In the two cases published by Valiaveedan et al. (8), midazolam was used for induction, rocuronium for intubation, and sevoflurane and fentanyl for maintenance without any problems.

CONCLUSION

The most effective management strategy to prevent hemolysis in patients known to have G6PD deficiency is to avoid oxidative stressors (6). Therefore, drugs used to relieve pain and anxiety should be those known to be safe or those that have not been shown to cause hemolytic crisis, such as benzodiazepines, codeine/codeine derivatives, propofol, fentanyl, and ketamine. Any person with a family history of hemolysis, African, Southern European, Middle Eastern, South East Asian, or central and Southern Pacific islander, and any person suspected of having G6PD deficiency should be screened for G6PD deficiency. A person with G6PD deficiency should avoid oxidative drugs and fava beans. Patients at risk

should be informed about the symptoms and signs of acute hemolytic crisis (cyanosis, headache, dyspnea, fatigue, lumbar/substernal pain, jaundice, scleral icterus, and dark brown urine). It should be kept in mind that laboratory findings of hemolysis may appear within 24-72 hours after exposure to the agent, before clinical findings, and that deepening of anemia may extend up to the 7th day. It is difficult to detect hemolytic crisis in day surgery or short-term hospitalizations (less than 24 hours). Therefore, the physician should inform high-risk patients and their relatives about the symptoms and findings of hemolytic crisis. In fact, a short telephone conversation with the patient after discharge will be beneficial for their health. If an acute hemolytic crisis is noticed in a patient, the patient must be hospitalized and monitored with a complete blood count of at least once a day to determine the need for blood transfusion. General anesthesia may mask early findings of hemolysis, and it is quite difficult to detect hemolytic crisis in an anesthetized patient. The presence of free Hb in plasma and urine is possible evidence of a hemolytic reaction. In treatment, the agent thought to cause hemolysis should be stopped immediately, and urine output should be ensured with crystalloid solutions and diuretics such as mannitol and/or furosemide (17).

Ethics

Informed Consent: The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for his/her/their images and other clinical information to be reported in the journal. The patient understand that her name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Footnotes

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Case Report

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Neuroleptic Malignant Syndrome Due to Antipsychotic Use in a Geriatric Case

Geriatrik Bir Olguda Antipsikotik Kullanımına Bağlı Gelişen Nöroleptik Malign Sendrom

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ABSTRACT

Neuroleptic malignant syndrome is a serious clinical condition that can develop due to antipsychotic use. In this case report, we discussed a 77-year-old patient with neuroleptic malignant syndrome. A 77-year-old female patient was admitted to the geriatric outpatient clinic with impaired oral intake, mental status change, reduced mobilization, and urinary incontinence that developed in the last week. The patient, who was using dual antipsychotics due to sleep problems, was hospitalized with the diagnosis of neuroleptic malignant syndrome presented with bilateral upper extremity rigidity. The patient, whose serum creatine kinase levels were high, was given intravenous hydration, clonazepam and bromocriptine treatments. A significant improvement was observed in her clinical condition with the treatment. The patient was discharged after 1 week of ward follow-up. Neuroleptic malignant syndrome is a rare clinical condition that can be overlooked. If not diagnosed, it can be fatal. Unnecessary antipsychotic use should be avoided, especially in the geriatric population, and treatment should be started as soon as possible after diagnosis.

Keywords: Antipsychotic, neuroleptic malignant syndrome, rigidity, creatine kinase, elderly

ÖZ

Nöroleptik malign sendrom, antipsikotik kullanımına bağlı olarak gelişebilen ciddi bir klinik durumdur. Bu olgu sunumunda, nöroleptik malign sendrom tanısı alan 77 yaşında bir hastayı ele aldık. Yetmiş yedi yaşında kadın hasta, son bir haftada gelişen oral alım bozukluğu, mental durum değişikliği, mobilizasyonda azalma ve üriner inkontinans şikayetiyle geriatri polikliniğine başvurdu. Uyku problemi nedeniyle ikili antipsikotik kullanan hastada bilateral üst ekstremitede rijidite mevcuttu ve nöroleptik malign sendrom tanısıyla hastaneye yatırıldı. Serum kreatin kinaz düzeyleri yüksek olan hastaya intravenöz hidrasyon, klonazepam ve bromokriptin tedavileri başlandı. Tedaviyle hastanın kliniğinde belirgin iyileşme gözlendi. Hasta, 1 haftalık servis takibinin ardından taburcu edildi. Nöroleptik malign sendrom, gözden kaçabilen nadir bir klinik durumdur. Tanı konulmadığı takdirde ölümcül olabilir. Özellikle geriatrik popülasyonda gereksiz antipsikotik kullanımından kaçınılmalı ve tanı konulduktan sonra mümkün olan en kısa sürede tedaviye başlanmalıdır.

Anahtar Kelimeler: Antipsikotik, nöroleptik malign sendrom, rijidite, kreatin kinaz, yaşlı

INTRODUCTION

A 77-year-old female patient with known dementia, cerebrovascular disease, hypertension, and epilepsy diagnoses applied to the geriatric outpatient clinic due to decreased oral intake, impaired mobilization, altered mental status, and urinary incontinence for the last week. On physical examination, bilateral rigidity was observed in the upper extremities. Muscle strength was 4/5 in the upper extremities and 2/5 in the lower extremities. Other system examinations were normal. Anamnesis revealed that she had been taking olanzapine 5 mg/day and quetiapin 50 mg/day for sleep disorders for the last 3-4 months. She was also taking memantine 20 mg/day, donepezil 5 mg/day, acetylsalicylic acid 100 mg/day, valsartan/hydrochlorothiazide 160/12.5 mg, and levetiracetam 1000 mg/day. Neuroleptic malignant syndrome (NMS) due to antipsychotic use was considered in the patient and she was admitted to the geriatric inpatient clinic. Vital signs showed a temperature of 36

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°C, blood pressure of 125/85 mmHg, pulse of 85/minute, and respiratory rate of 18/minute. The patient's baseline creatinine levels were 0.5 mg/dL, and when she was admitted to the clinic, her creatinine levels were 0.9 mg/dL. Creatine kinase (CK) levels were 408 U/L, C-reactive protein levels were 10 mg/L, and she had no leukocytosis. After the patient was admitted to the clinic, her CK level increased rapidly to 916 U/L. Serum electrolyte levels were normal. Brain magnetic resonance imaging showed chronic ischemic changes but no other pathology. There was no significant stenosis in carotid and vertebral Doppler ultrasonography. Olanzapine and quetiapine treatments were discontinued. A urinary catheter was inserted and intravenous hydration was started. Clonazepam 0.5 mg 3 times daily and bromocriptine 2.5 mg twice daily were started for 5 days. Due to acute kidney injury, the patient's valsartan/hydrochlorothiazide treatment was temporarily suspended. Oral nutritional support was provided. Mobilization exercises were performed under the supervision of a physiotherapist. With the current treatments, renal function tests returned to normal, and CK levels decreased to 36 U/L. Improvement was observed in the patient's oral intake and mental status. Rigidity in the upper extremities decreased and mobilization increased. Table 1 shows the patient's laboratory findings. The patient's general condition and laboratory results improved, and she was discharged from the geriatric inpatient clinic.

CASE REPORT

Neuroleptic Malignant Syndrome

NMS is a rare but potentially life-threatening condition associated with the use of antipsychotic medications. First-generation antipsychotic drugs carry a higher risk of NMS, but they can also occur with second-generation antipsychotics and other dopamine-blocking agents, such as antiemetics (1,2). NMS is not dose-dependent, although higher doses do increase the risk. Additionally, the withdrawal of levodopa or dopamine agonists or a relative deficiency of levodopa due to increased needs (such as during an infection) can also cause NMS (3).

The diagnostic criteria for NMS include a tetrad of symptoms: fever, altered mental status, rigidity, and autonomic instability. Hyperthermia is defined as core body temperature >38 °C (100.4 °F), muscle rigidity is often described as "lead-pipe", and autonomic dysfunction may manifest as tachycardia, hypertension or hypotension, diaphoresis, and incontinence. Mental status change may range from confusion to coma. Other supportive findings are elevated CK and liver transaminases due to muscle breakdown (rhabdomyolysis). CK is typically more than 1000 international units/L and can be as high as 100.000 international units/L (4). Rhabdomyolysis may also cause acute kidney injury. The exclusion of other causes, such as infections, metabolic disorders, or other drug-induced syndromes, also supports NMS diagnosis. The criteria for diagnosing disorders in the diagnostic and statistical manual of mental disorders (DSM V) include exposure to a dopamine-blocking agent within 72 hours prior to symptom development, severe muscle rigidity, and fever. Additionally, other minor criteria include diaphoresis, dysphagia, tremor, incontinence, altered level of consciousness, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, and elevated creatine phosphokinase (5). According to the severity of rigidity, confusion, heart rate and body temperature NMS can be classified as mild/early, moderate or severe (6). Mild NMS presents with mild stiffness, mild catatonia, or confusion, body temperature ⩽38 °C (100.4 °F), and heart rate ⩽100 bpm. Moderate NMS presents with moderate stiffness and worsening catatonia or confusion, body temperature 38 °C -40 °C (100.4 °F -104 °F), and heart rate 100-120 bpm. Severe NMS presents with severe stiffness, often leading to immobility; severe catatonia, confusion, or coma, body temperature ⩾40 °C (104 °F), and heart rate ⩾120 bpm.

DISCUSSION

NMS shares features with several other conditions, making differential diagnosis essential, including serotonin syndrome caused by serotonergic agents (e.g., SSRIs, SNRIs) differentiated by hyperreflexia, clonus, and gastrointestinal symptoms. Malignant hyperthermia is a condition triggered by anesthetic agents, often in genetically predisposed individuals. Central nervous system infections, such as meningitis or encephalitis, may present with fever and altered mental status. Heat stroke is differentiated by environmental exposure to high temperatures without muscle rigidity. Catatonia may present with rigidity and mutism but lacks autonomic instability and hyperthermia. Drug-induced parkinsonism has rigidity and bradykinesia without fever or autonomic dysfunction. The acute dystonic reaction has sudden muscle spasms without systemic symptoms. The anticholinergic syndrome can occur due to drug overdose, with patients often presenting symptoms such as encephalopathy and elevated body temperatures; however, these temperatures are typically not as severe as those seen in NMS. In contrast to NMS, features like diaphoresis, rigidity, and elevated CK levels are absent in anticholinergic syndrome. Instead, symptoms often atypical for NMS, such as flushing, mydriasis, and bladder distension, are commonly observed in these patients (6). In the present case, there was no history of catatonia, psychiatric illness except dementia and anesthetic agent or serotonergic agent exposure. Therefore, the diagnosis of NMS was considered.

The management of NMS involves immediately stopping the offending medication and providing supportive care. Additionally, dopamine agonists such as bromocriptine or amantadine can restore dopaminergic activity, while benzodiazepines may help reduce rigidity. It is also essential to reevaluate the use of antipsychotics and consider non-pharmacologic alternatives or switching to lower-risk medications if antipsychotics are necessary.

Table 1. Laboratory findings of the patient within days

Reference intervals	WBC ($3.8\text{-}11.8 \times 10^3/\mu L$)	CK (5-145 U/L)	AST (5-35 U/L)	LDH (5-248 U/L)	Creatinin (0.5-0.95 mg/dL)
Day 1	7.6	408	18	282	0.99
Day 2	8.8	916	40	255	0.92
Day 3	8.3	194	26	209	0.54
Day 4	8.3	82	21	217	0.54
Day 5	7.5	39	24	255	0.57

WBC: White blood cells, CK: Creatine kinase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase

An older woman with cognitive impairment was diagnosed in an outpatient setting while being treated concurrently with two atypical antipsychotic medications. She presented with symptoms of rigidity, urinary incontinence and impaired oral intake. A rapid increase in CK levels supported the diagnosis. Due to the timely intervention, she made a remarkable recovery.

CONCLUSION

Diagnosing NMS requires high clinical suspicion and awareness among healthcare providers. It is particularly concerning in older adults, who may be more susceptible to the side effects of antipsychotics due to age-related changes in pharmacokinetics and pharmacodynamics. Older adults often take multiple medications (polypharmacy), which increases the risk of drug interactions. Moreover, older adults tend to present with milder or atypical symptoms, leading to misdiagnosis or delayed diagnosis (7). They also face a higher risk of complications, such as renal failure and aspiration pneumonia, as well as increased mortality due to NMS.

Ethics

Informed Consent: Informed consent was obtained from the formal representatives of the patient. The information of the patient's identity was not defined in the manuscript.

Footnotes

Author Contributions

Surgical and Medical Practices: D.D.G., E.A.B., Concept: D.D.G., E.A.B., Design: D.D.G., E.A.B., Data Collection or Processing: D.D.G., E.A.B., Analysis or Interpretation: D.D.G., E.A.B., Literature Search: D.D.G., E.A.B., Writing: D.D.G., E.A.B.

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