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Investigation of the Level of Porphyria Disease Awareness in Primary Care Physicians

Birinci Basamak Hekimlerde Porfriya Hastalık Farkındalığı Düzeyinin Araştırılması

Aşkın Keskin KAPLAN[1], Gülbüz SEZGİN[2]

ABSTRACT

This study aimed to assess awareness of Porphyria Disease among primary care physicians and investigate its diagnosis and management. This study is a cross-sectional online survey conducted with the participation of 390 primary care physicians in Turkey. Participants were recruited through online platforms, including WhatsApp and email groups. Participants who provided consent were administered an online electronic survey created using Google Forms. Data were analyzed using IBM SPSS Statistics version 21.0. Ethical approval was granted by the Clinical Research Ethics Committee.

With an average of 14.13±9.56 years of medical experience, participants included 47.4% family medicine specialists, 38.5% family physicians, and 14.4% emergency medicine specialists. Only 10.5% of the total physicians reported evaluating patients with suspected Porphyria. Severe abdominal pain was the predominant symptom, cited by 78% of participants, while just 5.4% had previously been diagnosed with Porphyria. Notably, family medicine specialists exhibited a significantly higher inclination for both preliminary ($p<0.001$) and confirmed ($p=0.041$) porphyria diagnosis. 81.0% of physicians considered Familial Mediterranean Fever as part of their differential diagnosis when assessing patients with porphyria symptoms.

In conclusion, our study highlights an increased awareness of Porphyria among primary care physicians, likely owing to advancements in diagnostic methods. However, the need to raise awareness remains, given its crucial role in diagnosis. Therefore, it is essential to involve primary care physicians, particularly family medicine specialists and emergency medicine specialists, in porphyria education and awareness initiatives. These efforts can ensure accurate diagnoses and better care for patients affected by this rare disease.

Keywords: Awareness, Family medicine, Primary care, Porphyria disease

ÖZ

Bu çalışma, birinci basamak hekimleri arasında Porfiri Hastalığı farkındalığını, tanı ve tedavideki yaklaşımları araştırmayı amaçlamıştır.Bu çalışma, Türkiye'deki 390 birinci basamakta görev yapan hekimin katılımıyla gerçekleştirilen kesitsel bir çevrimiçi anket çalışmasıdır. WhatsApp ve e-posta grupları gibi çevrimiçi platformlar aracılığıyla Google Forms kullanılarak hazırlanan çevrimiçi elektronik anket ile katılımcılardan alınan onay sonrasında veriler toplanmıştır. Toplanan veriler, IBM SPSS Statistics sürüm 21.0 ile analiz edilmiştir. Bu çalışmaya Klinik Araştırma Etik Komitesi tarafından etik onay sağlanmıştır.

Ortalama 14,13±9,56 yıllık tıbbi deneyime sahip katılımcıların %47,4'ü aile hekimliği uzmanı, %38,5'i aile hekimi ve %14,4'ü acil tıp uzmanıydı.Toplam hekimlerin yalnızca %10,5'i ayırıcı tanıda porfiri hastalığını değerlendirdiğini bildirdi. birinci basamak hekimlerin %78'i tarafından şiddetli karın ağrısı en sık görülen semptom olarak belirtilirken daha önce porfiri tanısı koyduğunu hekimlerin %5,4'ü belirtmiştir.Özellikle Aile Hekimliğ uzmanlarının, aile hekimleri ve acil tıp uzmanlarına göre daha fazla porfiria öntanısı düşündüğü ($p<0.001$) ve porfiria tanısı koyduğu görüldü ($p=0.041$). Porfiri semptomları olan hastaları değerlendirirken hekimlerin %81,0'ı ise Ailesel Akdeniz Ateşini ayırıcı tanılarının bir parçası olarak değerlendirdi.

Sonuç olarak çalışmamız, tanı yöntemlerindeki gelişmelere bağlı olarak birinci basamak hekimleri arasında porfiri konusunda farkındalığın geçmiş yıllara göre artığı ancak porfiri hastalık farkındalığının tanıdaki hayati rolü göz önüne alındığında, çalışmamızda ortaya çıkan düşük oranın arttırılmasına duyulan ihtiyacın devam etiğini düşündürtmektedir. Bu bağlamda, birinci basamak hekimlerinin, özellikle aile hekimleri, aile hekimliği uzmanları ve acil tıp uzmanlarının porfiriya hastalığına yönelik eğitim ve farkındalık programlarına dahil edilmelerinin önemli olduğu düşünülmektedir.

Anahtar Kelimeler: Aile hekimliği, Birinci basamak sağlık hizmeti, Farkındalık, Porfiriya.

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[1] Dr.Öğr.Üyesi, Aşkın Keskin KAPLAN, Aile Hekimliği, Maltepe Üniversitesi Tıp Fakültesi, Aile Hekimliği Anabilim Dalı, e-posta: askinkkaplan@gmail.com, ORCID: 0000-0003-4326-1529

[2] Prof. Dr. Gülbüz SEZGIN, İç Hastalıkları, Maltepe Üniversitesi Tıp Fakültesi, İç Hastalılar Anabilim Dalı, e-posta: gulbuzsezgin@gmail.com, ORCID: 0000-0002-0774-2766

İletişim / Corresponding Author: Aşkın Keskin KAPLAN
e-posta/e-mail: askinkkaplan@gmail.com

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INTRODUCTION

Porphyrias are a group of rare and complex disorders caused by altered activity of the eight enzymes involved in heme biosynthesis.[1] They have a pan-ethnic distribution, with prevalence rates ranging from 0.5 to 10 per 100,000 in different populations.[2] Detecting Porphyria becomes relatively uncomplicated during the symptomatic phase through biochemical tests. However, these tests become less specific and sensitive during remission.[3,4]

The symptoms of porphyrias are diverse, including gastrointestinal distress, neurological disturbances, and dermatological manifestations.[5-7] The specific symptomatology can be different depending on the type of Porphyria, making accurate diagnosis challenging if not considered during the initial assessment of the patient.[8] Delays in diagnosis can have severe consequences, leading to increased morbidity and mortality rates.[6,7,9]

Among the porphyria variants commonly encountered in adults are Acute Intermittent Porphyria (AIP), Porphyria Cutanea Tarda (PCT), and Protoporphyria.[6,10,11] The estimated prevalence of Acute Intermittent Porphyria in Europe is 1/75,000.[7] Typical AIP attacks present with neurological findings, including acute abdominal pain, vomiting, muscle weakness, peripheral neuropathy, increased sympathetic activity (tachycardia, hypertension), and psychological symptoms. Respiratory failure may occur in rare cases, potentially leading to coma and death if left untreated.[12]

The affected enzyme, porphobilinogen deaminase, is usually reduced to 50% or less of normal activity. Notably, 90% of individuals carrying the disease genes do not develop symptoms. Attacks are triggered by external stimuli that induce heme synthesis in the liver, especially by drugs that induce mitochondrial cytochrome P-450.[13]

In contrast, PCT is a multifaceted disorder influenced by genetic and environmental factors. It typically presents blistering skin lesions on sun-exposed areas, liver dysfunction, and heightened photosensitivity. Another rare autosomal dominant porphyria, Protoporphyria, results from a deficiency in the ferrochelatase enzyme and is characterized by excruciating photosensitivity.[14]

In clinical practice, distinguishing Porphyria from other conditions can be challenging, with common differential diagnoses including FMF Disease (FMF), Acute Appendicitis, lead poisoning, and pesticide poisoning. [2,15,16] Porphyrias often manifest with life-threatening abdominal and neuropsychiatric symptoms, emphasizing the need for accurate and timely diagnosis. Remarkably, approximately 80% of patients with Porphyria can lead biochemically and clinically normal lives throughout their lifetimes.[2]

Despite the critical importance of prompt diagnosis and management, physicians frequently face a lack of awareness and knowledge regarding porphyria disorders.[17] This knowledge gap can lead to misdiagnoses and inappropriate treatments. Therefore, encouraging clinical suspicion and understanding of these rare disorders is essential in reducing diagnostic delays and improving outcomes for individuals affected by Porphyria.

Therefore, our study is designed to delve into the awareness levels of primary care physicians regarding Porphyria Disease. By shedding light on the current state of awareness among primary care providers, we also aim to contribute to the ongoing efforts to improve the detection and management of Porphyria.

MATERIALS AND METHOD

Study design and Sampling

This study utilized an online survey approach to assess the awareness of Porphyria Disease among primary care physicians in Turkey. Snowball sampling was employed to enhance the sample size within a three-month data collection period. The sample size of 380 participants was determined based on the population of primary care physicians in Turkey (N = 29,420), a 95% confidence level, and a 5% margin of error.

Data Collection

Participants were recruited through online platforms, including WhatsApp and email groups. Initial contact and consent were obtained through these online channels. Subsequently, participants who provided consent were administered an online electronic survey created using Google Forms.

Survey Instrument

The survey questionnaire consisted of three parts: An introductory section explaining the study's purpose and obtaining informed consent; demographic information, including age, gender, the field of specialization, tenure, and workplace; and the Porphyria awareness section, designed to evaluate participants' knowledge of Porphyria Disease.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 21.0. Categorical data were presented as numbers and percentages, while continuous variables were expressed as mean and standard deviation. The Chi-square test was utilized to compare categorical data, and the Mann-Whitney U test was used for data that did not exhibit a normal distribution ($p < 0.05$ was considered statistically significant).

Ethical Considerations

This study strictly adhered to ethical guidelines, including obtaining informed consent from all participants. The research protocol received approval from the University Clinical Research Ethics Committee, under reference number 2023/900/25, with an approval date of 2 May 2023. Measures were implemented to ensure data privacy and confidentiality throughout the study.

RESULTS AND DISCUSSION

The average length of time as a physician among the 390 participants in the study was 14.13±9.56 years. 47.4% of the participants were family medicine specialists. Only 10.5% of physicians stated that they evaluated their patients with a preliminary diagnosis of Porphyria. The most common symptom was severe abdominal pain, with 78%. Only 5.4% of physicians stated that they had diagnosed Porphyria before (Table 1).

Table 1. Distribution of participants by area of expertise, preliminary diagnosis and diagnostic status (n=390)

Variable	Category	N	%
Specialty	Emergency Medicine Specialist	55	14.1
	Family Physician	150	38.5
	Family Medicine Specialist	185	47.4
Consider Porphyria in differential diagnosis	No	349	89.5
	Yes	41	10.5
Symptoms*	Severe abdominal pain	32	78.0
	Dark urine (dark red-purple)	26	63.4
	Skin rashes in sun-exposed places since childhood	14	34.1
	Mental psychiatric disorder	5	12.2
Diagnosis of Porphyria	No	369	94.6
	Yes	21	5.4

* Multiple answers were given.

The average age of physicians who considered a preliminary diagnosis of Porphyria was found to be lower than that of those who did not (p=0.026). However, no significant difference was observed in reporting a diagnosis of Porphyria (p=0.731) (Table 2).

Table 2. Comparison of the participants' preliminary diagnosis and diagnosis of Porphyria according to the duration of their practice.

Variable	Category	Duration of practice (year) Meant±SD	p*
Preliminary diagnosis of Porphyria	No	14.60±9.81	0.026
	Yes	10.15±5.83	
Diagnosis of Porphyria	No	14.18±9.59	0.731
	Yes	13.29±9.21	

*Mann-Whitney U test, SD: Standard Deviation

Family medicine specialists showed a significantly higher tendency for both preliminary diagnosis (p<0.001) and confirmed diagnosis (p=0.041) of Porphyria compared to family physicians and emergency medicine specialists (Table 3).

Table 3: Specialty-based Comparison of Porphyria Prediagnosis and Diagnosis Among Participants.

Variable	Category	EMS	FP	FMS	p*
		n (%)	n (%)	n (%)	
Preliminary diagnosis of Porphyria	No	42 (12.0)	150 (43.0)	157 (45.0)	<0.001
	Yes	13 (31.7)	0 (0.00)	28 (68.3)	
Diagnosis of Porphyria	No	55 (14.9)	144 (39.0)	170 (46.1)	0.041
	Yes	0 (0.00)	6 (28.6)	15 (71.4)	

*Chi-squared test, EMS: Emergency Medicine Specialist, FP: Family Physician, FMS: Family Medicine Specialist.

Among the physicians who reported diagnosing Porphyria, 90.5% mentioned that they had diagnosed only one patient. Additionally, 76.2% of the patients received a porphyria diagnosis through the evaluation of porphyrin levels in 24-hour urine samples. Notably, 81.0% of physicians considered Familial Mediterranean Fever (FMF) as part of their differential diagnosis when assessing patients with porphyria symptoms. Interestingly, none of the physicians who reported diagnosing Porphyria stated that they did not provide treatment. (Table 4).

Table 4. Diagnosis, Differential Diagnosis, and Treatment by Physicians (n=21) in Porphyria Cases.

Variable	Category	N	%
Number of porphyria patients diagnosed	1	19	90.5
	2	2	9.5
Method of diagnosing Porphyria *	Porphyrin level in 24-hour urine	16	76.2
	Detection of porphobilinogen in urine with Erlich reagent (Watson - Swartz test)	3	14.3
	Detection of porphobilinogen in urine with Erlich reagent (Watson - Swartz test) Porphyrin level in 24-hour urine	2	9.5
Diseases considered in differential diagnosis*	FMF (Familial Mediterranean Fever)	17	81.0
	Appendicitis	8	38.1
	Lead Poisoning	8	38.1
	Polycystic Ovary Syndrome	2	9.5
	Inflammatory Bowel Disease (IBS)	14	66.7
Treatment of Porphyria	No	21	100

* Multiple answers were given.

Porphyria is rare compared to other common diseases and can be misdiagnosed, particularly among primary care physicians, as the symptoms are usually nonspecific.[2] These misdiagnoses may lead patients to undergo unnecessary medical treatments, including surgical interventions, thus increasing the risk of complications for the patients and pose life-threatening results.[18] Also, lack of specificity of symptoms can lead to misdiagnosis and a delay of the diagnosis, which was found in one study showing an average 15-year delay from symptom onset to diagnosis.[18]

We assessed the awareness of porphyria disease among primary healthcare physicians, with a particular emphasis on family medicine specialists and emergency medicine specialists, as awareness of Porphyria has been shown to play a pivotal role in the early diagnosis of this rare disease.[19] In this study, 47.4% of the 390 participants were family medicine specialists, and 10.5% of these participants stated that they evaluated their patients with a preliminary diagnosis of Porphyria. The most common symptom was severe abdominal pain, with a rate of 78%, which was similarly observed in other studies and patient series.[2,5,20,21] Porphyria disease is often diagnosed late or misdiagnosed and may end up with unnecessary surgical interventions. In this case, patients may undergo surgery unnecessarily, as they may need to undergo surgical operations. In one patient series, more than 60% of patients experiencing Intermittent Acute Porphyria attacks underwent appendectomy surgery.[18]

Our study shows a relationship between physician experience and age in diagnosing Porphyria. Physicians are more likely to consider Porphyria in the differential diagnosis when people are younger. This may be a result of improved biochemical tests for Porphyria and increased awareness of the disease. However, the fact that physicians do not differ in working experience and that they diagnose Porphyria relatively rarely can be explained by the rare occurrence of the disease. All these factors highlight the importance of better understanding and implementation of the diagnosis and treatment of porphyria disease among primary care providers.

Our study observed that family medicine specialists considered and diagnosed Porphyria more frequently than family physicians and emergency medicine specialists ($p<0.001$). This highlights the necessity of a multidisciplinary approach in diagnosing porphyria disease. In addition, it may suggest that family medicine specialists are more conscious in this field because they have undergone multidisciplinary training such as general surgery, internal medicine, and emergency medicine at a higher rate than other medical specialties.

In our study, 90.5% of the physicians who diagnosed Porphyria diagnosed only one patient, and 76.2% stated that they examined the porphyrin levels in the patients' 24-hour urine to diagnose Porphyria. This shows that due to the rarity of porphyria disease, it is possible to diagnose it in only a few patients.[2] However, looking at the porphyrin level in 24-hour urine to diagnose Porphyria is another finding emphasizing awareness's importance in differential diagnosis. 81.0% of the physicians who considered porphyria disease in the differential diagnosis stated that they considered FMF (Familial Mediterranean Fever) disease. This shows that in the geography where the study was conducted, patients with similar symptoms first appear before physicians with suspicion of FMF. Since severe abdominal pain is often seen in FMF symptoms, it can be thought that this is why patients apply to the hospital. None of the physicians who diagnosed Porphyria stated that they applied porphyria treatment. This situation shows how porphyria treatment is carried out in private centers but how critical it is for the diagnosis to be made by primary healthcare providers. In general, in our study, the awareness of Porphyria among physicians providing primary care was 10.5%, but with the diagnostic methods that have improved compared to previous years, there is a

significant increase in the diagnosis of the disease. It is possible to state that awareness has increased in parallel with the increase in information. These difficulties in diagnosing and treating porphyria disease show how critical it is for healthcare professionals, especially primary healthcare providers, to increase their awareness of this disease and correctly guide their patients. In general, patients should be considered in the differential diagnosis of rare diseases such as Porphyria when severe symptoms may not be specific.

In this context, increasing awareness of Porphyria disease among primary care providers is critical to ensure that patients receive an accurate diagnosis and reduce the risk of complications. The results of our study confirm the need to increase awareness of porphyria disease and encourage more effective collaboration among healthcare professionals in diagnosing and treating this rare disease.

Study limitations

Although we reached the required number statistically in our study, the need for more samples in subgroup analyses can be seen as a limitation. Apart from this, the fact that the online method was used in the study methodology can also be considered a limitation.

CONCLUSION AND RECOMMENDATIONS

This study shows that due to the rarity of porphyria disease and the non-specificity of its symptoms, correct diagnosis may be delayed, and patients may be subjected to unnecessary treatments. It is understood that the diagnosis of Porphyria disease is of great importance, especially for primary healthcare providers, family physicians, family medicine specialists, and emergency medicine specialists.

Our study demonstrates the need to increase awareness of porphyria disease among healthcare professionals. Although patients' severe symptoms are not specific, it is necessary to consider the differential diagnosis of potential threats of rare diseases. In this context, it is essential to include primary care physicians, especially family physicians, family medicine specialists, and emergency medicine specialists, in education and awareness programs for porphyria disease. Such education and awareness-raising efforts can ensure that patients receive accurate diagnoses and prevent unnecessary surgical interventions. As a result, diagnosis and treatment of porphyria disease require more effective collaboration between primary care providers, and the presence of nonspecific symptoms in patients should prompt consideration of rare diseases like Porphyria in the diagnostic process.

The results of this study suggest that closer collaboration between healthcare professionals should be encouraged to make the differential diagnosis of porphyria disease more quickly and accurately.

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