Turkish Journal of Geriatrics
2017;20 (3):187-193

- Ahu YORULMAZ[1]
- Duru TABANLIOĞLU ONAN[1]
- Seray KULCU ÇAKMAK[1]
- Başak YALÇIN[1]

Correspondance

Ahu YORULMAZ
Ankara Numune Training and Research Hospital,
Dermatology Clnic,
ANKARA

Phone: 3125084000
e-mail: ahuyor@gmail.com

Received: 25/05/2017
Accepted: 10/08/2017

[1] Ankara Numune Training and Research Hospital,
Dermatology Clnic,
ANKARA

RESEARCH

A RETROSPECTIVE STUDY ON THE ETIOLOGICAL FACTORS OF CHRONIC PRURITUS IN THE ELDERLY

Abstract

Introduction: Pruritus, a common symptom in the elderly, is usually a chronic condition lasting for more than 6 weeks. Chronic pruritus in the elderly may be caused by systemic diseases, including renal diseases, iron deficiency anemia, parasitoses, hepatobiliary diseases, leukemia, lymphomas, and endocrine disorders. In this retrospective study, we aimed to investigate the relationship of systemic diseases with chronic pruritus in the elderly.

Materials and Method: Descriptive statistics were computed for means, standard deviations, and frequencies. The chi-square test or Fisher's exact test was used for statistical analysis, with a significance threshold of $p<0.05$.

Results: Totally, 631 consecutive patients [307 males and 324 females; mean age, 73.34±6.49 years (range, 65–95 years)] were enrolled. In 292 patients, at least one laboratory test was performed to identify the etiology of chronic pruritus. In 42 patients, abnormal laboratory test results led to the diagnosis of a pruritus-related systemic disease. This study revealed that 21 patients had iron deficiency anemia, 2 had solid malignancies, 7 had hypothyroidism, 8 had renal disease, and 5 had hepatobiliary diseases. There was a statistically significant relationship between performing laboratory tests for chronic pruritus and detecting a pruritus-related systemic disease ($p<0.001$).

Conclusion: Chronic pruritus in the elderly poses a diagnostic challenge. Our study showed that chronic pruritus may be a manifestation of an underlying systemic disease. Therefore, we suggest that multiple etiologies should be considered based on relevant clinical and investigational data.

Key Words: Pruritus; Aged; Laboratories

ARAŞTIRMA

YAŞLILARDA GÖRÜLEN KRONİK PRURİTUS ETİYOLOJİSİ ÜZERİNE RETROSPEKTİF BİR ÇALIŞMA

Öz

Giriş: Yaşlılarda sık karşılaşılan bir semptom olan kaşıntı, genellikle 6 haftadan uzun süren kronik bir durumdur. Yaşlılarda görülen kronik kaşıntı, böbrek hastalıkları, demir eksikliği anemisi, parazitozlar, hepatobiliyer hastalıklar, lösemi, lenfomalar ve endokrinolojik hastalıkları içeren çok sayıda sistemik hastalıkla ilişkili olabilir. Bu retrospektif çalışmada, yaşlılarda görülen kronik kaşıntı ile sistemik hastalıkların ilişkisini araştırmayı hedefledik.

Gereç ve Yöntem: Çalışmada ortalama, standart sapma ve frekans değerleri için betimsel analiz yapıldı. İstatistiksel karşılaştırmalarda ki-kare veya Fisher kesin ki-kare test kullanıldı. $p<0.05$ olan değerler istatistiksel olarak anlamlı kabul edildi.

Bulgular: Toplamda 631 ardışık hasta [307 erkek ve 324 kadın; ortalama yaş, 73.34±6.49 yıl (dağılım, 65–95 yıl)] değerlendirildi. 292 hastada kronik pruritus etiyolojisini saptamak amacıyla en az bir laboratuvar testi yapıldı. 42 hastada patolojik olarak sonuçlanan laboratuvar testleri pruritus ilişkili sistemik hastalığın tanısının konmasına yol açtı. Bu çalışma ile 21 hastada demir eksikliği anemisi, 2 hastada solid malignite, 7 hastada hipotiroidizm, 8 hastada böbrek hastalığı ve 5 hastada hepatobiliyer hastalık tespit edildi. Kronik pruritus için laboratuvar tetkiki yapmak ile pruritus ilişkili sistemik hastalık tespiti arasında istatiksel olarak anlamlı ilişki saptandı ($p<0.001$).

Sonuç: Yaşlılarda görülen kronik pruritus tanı koyma bakımından güç bir durumdur. Çalışmamız, kronik pruritusun altta yatan sistemik bir hastalığın bulgusu olabileceğini göstermiştir. Bu nedenle, uygun klinik ve laboratuvar veriler doğrultusunda çok sayıda etiyolojinin göz önünde bulundurulması gerektiği düşünülmektedir.

Anahtar Sözcükler: Pruritus; Yaşlı; Laboratuvar

INTRODUCTION

Pruritus or itching has been defined as "the unpleasant skin sensation that frequently provokes scratching'(1). It is a highly prevalent and clinically relevant symptom in dermatology (2). Chronic pruritus refers to daily/almost daily itching lasting for more than 6 weeks (3,4). Beyond dermatologic disorders, chronic pruritus is associated with systemic diseases,including renal diseases, iron deficiency anemia, parasitoses, hepatobiliary diseases, human immunodeficiency virusinfection, brain tumors, polycythemia vera, leukemia, lymphomas, and endocrine disorders (1,3-5). In the literature, there are multiple studies that have investigated the role of systemic factors in the etiology of chronic pruritus (6-11). However, to our knowledge, there are inadequate data on the role of systemic diseases in the etiopathogenesis of chronic pruritus in the elderly. In this retrospective study, we aimed to investigate the role of systemic factors in the etiopathogenesis of chronic pruritus in the elderly.

MATERIALS AND METHOD

We retrospectively reviewed the medical records of patients aged ≥65 years who were treated at our institution between April 2015 and April 2016 with a diagnosis of chronic pruritus. We recorded data from the hospital patient charts after ensuring consistency with the study protocol. The study was conducted in accordance with the Declaration of Helsinki and was approved by the medical ethical committee of Ankara Numune Research and Education Hospital, Turkey (Protocol no: 2016-1179). All of the patients met the inclusion and exclusion criteria of the study. Inclusion criteria were the clinical diagnosis of chronic pruritus with a duration of more than 6 weeks and no history of primary skin lesions. We only included patients whom diagnosis of chronic pruritus was made in the dermatology department. We excluded patients with a prior history of a pruritus-related systemic disease. Patients with dermatoses with acute pruritus were not considered within the study. Data obtained from the records included age, sex, accompanying diseases, and if present, laboratory workups for chronic pruritus and the outcomes of these laboratory tests. Laboratory workups that had been selected in order to exclude underlying etiologic factors in chronic pruritus were without a standart protocole, each test reflect the preference of the individual doctor working at the department.

A detailed statistical analysis was made based on the acquired retrospective data. Statistical analysis was performed using SPSS software, Version 18 (SPSS Inc., Chicago IL, USA). Frequencies were calculated for variables related to demographic and clinical patient characteristics. Age was described as mean±standard deviation and range. The chi-square test or Fisher's exact test was conducted to determine statistical associations between performing laboratory tests for pruritus and detecting a pruritus-related disease. A p-value of <0.05 was considered statistically significant.

RESULTS

Totally, 631 consecutive patients [307 males (48.7%) and 324 females (51.3%); mean age, 73.34±6.49 years (range, 65–95 years)] were enrolled. There was a history of at least one medical problem in 64.5% of the patients (n=407). Table 1 shows the frequencies of accompanying diseases in the study group. In 46.3% of the patients (n=292), at least one laboratory test was performed to identify the etiology of chronic pruritus. Table 2 shows the frequency of laboratory tests performed, and Table 3 demonstrates the frequency of abnormal results obtained from laboratory tests. In 6.7% of the patients (n=42), abnormal results obtained from laboratory tests led to the diagnosis of a pruritus-related systemic disease. In total, 3.3% of the patients (n=21) had iron deficiency anemia, 0.3% (n=2) had solid malignancies, 1.1% (n=7) had hypothyroidism, 1.3% (n=8) had renal disease, and 0.8% (n=5) had hepatobiliary diseases.

A statistically significant relationship was found between performing laboratory tests for chronic pruritus and detecting a pruritus-related disease ($p<0.001$). Among patients who had undergone laboratory tests, 13.4% were diagnosed with a pruritus-related disease. In addition, 92.9% ofthe patients eventually diagnosed with a pruritus-related disease had undergone laboratory tests. Statistically significant relationships were observed between performing laboratory tests and detectingiron deficiency anemia, hypothyroidism, and hepatic and biliary disorders ($p<0.001$, $p=0.004$, and $p=0.021$, respectively). There were no statistically significant relationships between performing laboratory tests and detecting a solid malignancy ($p=0.214$) or renal disease ($p=0.153$).

DISCUSSION

Pruritus is one of the most common dermatological complaints. However, it can be the marker of a systemic disorder (1,3,4). In the literature, there are reports that have described a causal link between pruritus and systemic diseases (5,9-11). In the present retrospective study, we aimed to investigate this causal relationship in an elderly population. We retrospectively reviewed medical records in our hospital and found that 46.3% of the patients underwent at least one laboratory test to identify the etiology of chronic pruritus. In 6.7% of the patients, abnormal results from laboratory tests led to the diagnosis of a pruritus-related systemic disease, including iron deficiency anemia, solid malignancy, hypothyroidism, renal disease, and hepatobiliary diseases.

Iron deficiency anemia was the most common pruritus-related systemic disease in our study. A number of other hematologic diseases, including polycythemia vera, hemochromatosis, leukemia, Hodgkin's lymphoma, and myeloma, have been reported to be are associated with pruritus. In contrast to other hematologic diseases, little is known about the biochemical mechanisms involved in the pathophysiology of anemia-related pruritus (1,5,12,13). However, even in the absence of anemia, pruritus is a prevalent symptom and iron replacement therapy typically resolves anemia-related pruritus within weeks (1,12,14). It has been suggested that there is a link between malignancy, malignancy-related anemia, and anemia-related pruritus (1). Tumors cause pruritus not only because of anemia but also because of the release of endogenous compounds, including opioids and cytokines. Paraneoplastic pruritus has been defined as chronic pruritus that is a sign of malignancy. Pruritus of lymphoma is a well-known prototype of paraneoplastic pruritus, but solid tumors may also cause intractable pruritus (15). In the present study, we demonstrated that chronic pruritus is associated with a solid malignancy in 0.3% of patients.

It is well established that hypothyroidism is associated with chronic pruritus. It is postulated that dry skin (xerosis) in hypothyroidism is the result of decreased sebaceous gland activity, decreased sweat secretion, and low epidermal sterol synthesis (1,5,13). In elderly patients, dry skin is one of the most common dermatological conditions. With advancing age, skin water content and sebum production decrease but the number and size of corneocytes increase, which are the primary cell type in the stratum corneum, the outermost part of the epidermis (16). Apparently, both hypothyroidism and evident changes associated with advancing age contribute to hypothyroidism-associated pruritus in the elderly. In 1.1% of the patients in the present study, hypothyroidism led to pruritus.

Renal diseases and hepatobiliary diseases are other pruritus-related diseases detected in the present study. Uremia is one of the most important systemic causes of generalized pruritus. It has been suggested that uremic pruritus affects 50–90% of patients undergoing dialysis (17). The exact pathogenic basis of pruritus in renal failure is unknown. However, it is wellknown that uremic pruritus only occurs in chronic renal failure and that renal failure must be severe to be associated with pruritus. Uremic xerosis, secondary hyperparathyroidism, hypervitaminosis A, uremic neuropathy, elevated serum histamine levels, and uremic toxins have been described as factors triggering uremic pruritus (17-19).

Table 1. Frequencies of accompanying diseases in the study group.

Diseases	***n***	**%**
Cardiovascular diseases	205	32.5
Neuropsychiatric disorders	63	10.0
Solid malignancy	4	0.6
History of solid malignancy	11	1.7
Gastrointestinal diseases	29	4.6
Diabetes mellitus	83	13.2
Renal insufficiency	14	2.2
Hypo/hyperthyroidism	31	4.9
Pulmonary diseases	21	3.3
Leukaemia/ lymphoma/ myeloma	3	0.5
Anemia	5	0.8
Nutritional deficiencies	2	0.3
Coagulopathies	2	0.3
Other (cataracts, glaucoma, hemorrhoid, osteoporosis, gonartrosis, allergic rhinitis/ conjunctivitis, psoriasis, nefrolitiasis, benign prostatic hyperplasia, rheumatoid arthritis)	93	14.7

Pruritus is a common symptom of cholestatic, hepatobiliary diseases. Both intra- and extrahepatic cholestatic diseases may cause pruritus, including primary biliary cirrhosis, primary sclerosing cholangitis, chronic hepatitis B and C, carcinoma of the bile ducts, alcoholic cirrhosis, and autoimmune hepatitis. Although the exact underlying pathogenic mechanisms remain unknown, lysophosphatidic acid, bile salts, opioids, histamine, and progesterone metabolites may be involved in the development of cholestatic pruritus (1,5,9,20). Clearly, there are numerous mechanisms involved in the pathogenesis of pruritus-related diseases. In this study, we investigated the role of systemic factors in the etiopathogenesis of chronic pruritus in the elderly. We retrospectively reviewed medical records to determine the percentage of patients who had undergone laboratory tests and the outcomes of these laboratory tests.

In this study, we found a statistically significant relationship between performing laboratory tests for chronic pruritus and detecting a pruritus-related disease. Overall, abnormal laboratory test results led to the diagnosis of a pruritus-related systemic disease in 6.7% of the patients. There are numerous underlying factors for chronic pruritus that necessiate detailed laboratory

analysis. As seen in Table 2, we performed several laboratory tests. Although some advanced tests, such as protein electrophoresis and determining antinuclear antibody and total immunoglobulin E concentrations, were performed in a small number of patients, the total number of tests performed is not negligible. Of note, we did not perform associated laboratory tests in patients with a history of pruritus-related disease. Therefore, our results reflect newly diagnosed hypothyroidism, anemia, malignancy, hepatobiliary diseases, or renal insufficiency.

On the other hand, there are limitations of our study. One of the most important limitation is that laboratory analysis that had been selected for patients were without a standard protocole, each test reflect the preference of the individual doctor working at the department. But, the study was not designed prospectively, therefore as a retrospective study, we are only left to conclude from the available data. Although the main goal of this study was to investigate the role of systemic factors in the etiopathogenesis of chronic pruritus, we also planned to reveal the preferences of clinicians dealing with chronic pruritus and whether or not it is worth performing detailed laboratory investigations also what are the proportions of each performed laboratory tests. Furthermore, there is an another major limitation for this study. Some of the advanced tests, such as protein electrophoresis and determining antinuclear antibody and total immunoglobulin E concentrations, were performed only in a small number of patients, which might cause suspicion about the appropriateness of the interpretation of the statistical analysis.

We suggest that our study contributes to the existing literature. We have shown that although it seems to be demanding, a comprehensive investigation should be carried out in every patient with chronic pruritus. Indeed, history and physical examination are the main components of the evaluation of a patient. In this study, we included patients whom diagnosis was made through a stepwise approach. We excluded patients with a preexisting pruritus-related disease and dermatoses with pruritus. Also we took a detailed drug history. It is wellknown that elderly patients frequently use drugs that might be the real cause of chronic pruritus. Therefore, our results reflect newly diagnosed diseases, indicating the importance of investigation for chronic pruritus.

Chronic pruritus is a common problem in the elderly. In everyday practice, dermatologists encounter senile people with chronic pruritus. There should be an algorithm to determine which patients should undergo detailed laboratory tests. In the literature, there are an inadequate number of studies on the relationship of systemic diseases with chronic pruritus in the elderly (21). We believe that our study will enrich the limited data available on the relationship between systemic diseases and chronic pruritus in the elderly. It is important to note that the laboratory tests in our patients were detailed. The financial impact of these investigations should be considered. In conclusion, we recommend a comprehensive evaluation for all elderly patients with chronic pruritus. History, physical examination and laboratory investigations should be the mainstay of this evaluation. Further studies are needed to elucidate the relationship between systemic diseases and chronic pruritus in the elderly and to determine the best algorithm for assessing which laboratory tests are necessary.

Conflicts of Interest

The authors declare no conflict of interest.

Table 2. Laboratory investigations and results.

Laboratory tests			Pathological laboratory results		
	n	%		n	%
Complete blood count	281	44.5	Anemia	72	11.4
			Polycythemia	1	0.2
			Thrombocytopenia	12	1.9
			Thrombocytosis	2	0.3
			Leukocytosis	15	2.4
			Eosinophilia	41	6.5
			Leukopenia	20	3.2
Sedimentation	178	28.2		54	8.6
C-reactive protein	156	24.7		44	7.0
Rheumatoid factor	21	3.3		8	1.3
Blood urea nitrogen	284	45.0		59	9.4
Alanine aminotransferase	282	44.7		10	1.6
Aspartate aminotransferase	279	44.2		7	1.1
Gamma-glutamyl transferase	248	39.3		21	3.3
Total protein	95	15.1		3	0.5
Sodium	132	20.9		8	1.3
Potassium	125	19.8		8	1.3
Parathyroid hormone	129	20.4		17	2.7
Folate	33	5.2		2	1.3
25-hydroxyvitamin D	69	10.9		34	5.4
Prostate specific antigen	113	17.9		19	3.0
Hepatitis B and C serology	90	14.3		36	5.7
Fecal occult blood test	91	14.4		8	
Total immunoglobulin E	11	1.7		4	0.6
Antinuclear antibodies	21	3.3		2	0.3
Peripheral blood smear	174	27.6		34	5.4
Anti-streptolysin O	19	3.0		3	0.5
Fasting blood glucose	264	41.8		62	9.8
Creatinine	288	45.6		36	5.7
Uric acid	49	7.8		12	1.9
Alkaline phosphatase	232	36.8		18	2.9
Albumin	107	17.0		7	1.1
Calcium	150	23.8		6	1.0
Ferritin	144	22.8		20	3.2
Thyroid function test	154	24.4		34	5.4
Thyroid autoantibodies	96	15.2		15	2.4
Vitamin B_{12}	76	12.0		3	0.5
Human immunodeficiency virus screening	50	7.9		6	1.0
Stool parasite testing	65	10.3		1	0.2
Protein electrophoresis	8	1.3		-	-
Total iron binding capacity	169	26.8		20	3.2

REFERENCES

1. Yonova D. Pruritus in certain internal diseases. Hippokratia 2007;11:67-71. (PMID:19582180).
2. Kopyciok ME, Ständer HF, Osada N, Steinke S, Ständer S. Prevalence and characteristics of pruritus: a one-week cross-sectional study in a German dermatology practice.Acta Derm Venereol 2016;96:50-5. (PMID:26067841).
3. Rajagopalan M, Saraswat A, Godse K, Shankar DS, Kandhari S, Shenoi SD, et al. Diagnosis and Management of Chronic Pruritus: An Expert Consensus Review. Indian J Dermatol 2017;62:7-17. (PMID:28216719).
4. Grundmann S, Ständer S. Chronic pruritus: clinics and treatment. Ann Dermatol 2011;23:1-11. (PMID:21738356).
5. Khopkar U, Pande S. Etiopathogenesis of pruritus due to systemic causes: Implications for treatment. Indian J Dermatol Venereol Leprol 2007;73:215-7. (PMID:17675726).
6. Zirwas MJ, Seraly MP. Pruritus of unknown origin: a retrospective study. J Am Acad Dermatol 2001;45:892-6. (PMID:11712035).
7. Weisshaar E, Apfelbacher C, Jäger G, Zimmermann E, Bruckner T, Diepgen TL, et al. Pruritus as a leading symptom: clinical characteristics and quality of life in German and Ugandan patients. Br J Dermatol 2006;155:957-64. (PMID:17034525).
8. Polat M, Oztas P, Ilhan MN, Yalçin B, Alli N. Generalized pruritus: a prospective study concerning etiology. Am J Clin Dermatol 2008;9:39-44. (PMID:18092842).
9. Chia SC, Bergasa NV, Kleiner DE, Goodman Z, Hoofnagle JH, Di Bisceglie AM. Pruritus as a presenting symptom of chronic hepatitis C. Dig Dis Sci 1998;43:2177-83. (PMID:9790451).
10. Murphy M, Carmichael AJ. Renal itch. Clin Exp Dermatol 2000;25:103-6. (PMID:10733630).
11. Neilly JB, Martin A, Simpson N, MacCuish AC. Pruritus in diabetes mellitus: investigation of prevalence and correlation with diabetes control. Diabetes Care 1986;9:273-5 .(PMID:3731993).
12. Cohen KR, Frank J, Salbu RL, Israel I. Pruritus in the elderly: clinical approaches to the improvement of quality of life. P T 2012;37:227-39. (PMID:22593635).
13. Tivoli YA, Rubenstein RM. Pruritus: an updated look at an old problem. J Clin Aesthet Dermatol 2009;2:30-6. (PMID:20729968).
14. Stäubli M.Pruritus--a little known iron-deficiency symptom. Schweiz Med Wochenschr 1981;111:1394-8. (PMID:7280639).
15. Yosipovitch G. Chronic pruritus: a paraneoplastic sign. Dermatol Ther 2010;23:590-6. (PMID:21054705).
16. Yorulmaz A, Yalcin B. Investigating the frequency of dermatological diseases in the oldest old. Turkish Journal of Geriatrics 2016;19 (4):211-6.
17. Attia EA, Hassan AA. Uremic pruritus pathogenesis, revisited. Arab J Nephrol Transplant 2014;7:91-6. (PMID:25366503).
18. Berger TG, Steinhoff M. Pruritus and renal failure. Semin Cutan Med Surg 2011;30:99-100. (PMID:21767770).
19. Mettang T, Kremer AE. Uremic pruritus. Kidney Int 2015;87:685-91. (PMID:24402092).
20. Imam MH, Gossard AA, Sinakos E, Lindor KD. Pathogenesis and management of pruritus in cholestatic liver disease. J Gastroenterol Hepatol 2012;27:1150-8. (PMID:22413872).
21. Sliti N, Benmously R, Fenniche S, Marrak H, Ben Jannet S, Mokhtar I.Pruritus in the elderly: an epidemic-clinical study (about 208 cases). Tunis Med 2011;89:347-9. (PMID:21484683).