Received: 14 May 2024 | **Accepted:** 12 June 2024 **Genel Tıp Derg. Volume** 34/**Issue** 3 (June), 408-412
DOI: 10.54005/geneltip.1482802

ORIGINAL ARTICLE

Evaluation of Stroke Patients Diagnosed with Rheumatologic Diseases

İnme Geçiren Romatolojik Hastalık Tanılı Hastaların Değerlendirilmesi

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How to cite ?

Özgüncü C, Öztürk Ş, Özdemir G. Evaluation of Stroke Patients Diagnosed with Rheumatologic Diseases. Genel Tıp Derg. 2024;34(3):408-12.

ABSTRACT

Objectives: Some comorbid diseases are recognized as specific risk factors for stroke. Rheumatological diseases constitute an important group of these diseases. In our study, we evaluated patients who were followed up for stroke in our clinic. We included patients with additional rheumatological diagnoses in a separate group and attempted to determine their differences from patients without a diagnosis. In this way, we aimed to investigate the effect of rheumatological comorbidity on prognosis in stroke patients.
Material and methods: In the study, we included patients who were admitted to our hospital between 2016-2020, and diagnosed with ischemic stroke, hemorrhagic stroke, transient ischemic attack, hemorrhagic infarction, and were hospitalized. Age, gender, stroke subtype, need for intensive care and exitus status of these patients were recorded. We compared patients with a rheumatological diagnosis to patients with other stroke diagnoses using appropriate statistical methods.
Results: 2053 patients with an average age of 66.22±14.33 participated in the study. A total of 37 patients were diagnosed with at least 1 rheumatological disease. We calculated the average age of these patients as 51.62±15.88. Compared to patients without a diagnosis of rheumatological disease, the age was significantly lower($p<0.001$). However, we did not find a significant relationship between the distribution of stroke subtypes($p=0.538$), and there was no significant difference in terms of gender($p=0.149$). No statistical significance was observed in intensive care unit admissions and exitus rates. ($p=0.384,0.868$)
Conclusion: Some rheumatologic diseases are known to be linked to stroke risk. In our study, we did not observe a significant difference between the groups in terms of prognosis. Having a history of stroke is an independent risk factor for developing stroke in the future. We believe that since patients with a rheumatological diagnosis have a stroke at a younger age, their risk of a subsequent stroke increases, and their follow-up should be more frequent.

Keywords: Neurology, Rheumatological diseases, Stroke, Ischemic stroke

ÖZ

Amaç: Komorbid hastalıkların bazılarının inme için özellikle risk faktörü olduğu bilinmektedir. Bu hastalıklar içinde önemli bir grubu da romatolojik hastalıklar oluşturmaktadır. Çalışmamızda kliniğimizde inme nedeni ile takip edilen hastalar değerlendirilmiş ek romatolojik tanısı bulunan hastalar ayrı bir gruba alınarak tanısı olmayan hastalardan farklılıkları saptanmaya çalışılmıştır. Bu sayede inme hastalarında romatolojik komorbiditenin prognoz üzerine etkisini araştırmayı amaçlıyoruz.
Gereç ve Yöntem: Çalışmaya 2016-2020 tarihleri arasında hastanemize başvuran ve yatırılarak takip edilen iskemik inme, hemorajik inme, geçici iskemik atak, hemorajik enfarkt tanılı hastalar dahil edildi. Bu hastaların yaş, cinsiyet, inme alttipi, komorbid hastalık alttipi, yoğun bakım ihtiyacı, exitus durumları kayıt altına alındı. Romatolojik tanıya sahip olan hastalar diğer inme tanılı hastalarla uygun istatistiksel yöntemler kullanılarak karşılaştırıldı.
Bulgular: Çalışmaya yaş ortalaması 66.22±14.33 olan 2053 hasta katıldı. Bu hastaların 37 tanesinde en az 1 romatolojik hastalık tanısı bulunmaktaydı. Bu hastaların yaş ortalaması 51.62±15.88 olarak hesaplandı. Romatolojik hastalık tanısı bulunmayan hastalarla kıyaslandığında yaş anlamlı olarak daha düşük izlendi ($p<0.001$). Ancak inme alttiplerinin dağılımı açısından anlamlı ilişki yoktu($p=0.538$), cinsiyetler açısından anlamlı farklılık izlenmedi($p=0.149$). Yoğun bakım yatışları ve exitus oranları arasında istatistiksel anlamlılık yoktu ($p=0.384,0.868$).
Sonuç: Bazı romatolojik hastalıkların inme için risk faktörü olduğu bilinmektedir. Çalışmamızda prognoz açısından gruplar arası belirgin farklılık izlenmedi. Bu nedenle romatolojik tanısı bulunan hastaların inme prognozu genel popülasyonla benzer olarak değerlendirilebilir. Geçmişinde inme öyküsü olması gelecekte inme gelişmesi açısında bağımsız bir risk faktörüdür. Romatolojik tanısı bulunan hastaların daha genç yaşta inme geçirmeleri nedeniyle bir sonraki inme açısından riskleri artmakta ve takiplerinin daha sık olması gerektiği kanaatindeyiz.

Anahtar Kelimeler: nöroloji, romatolojik hastalıklar, inme, iskemik inme

Introduction

Stroke is one of the most common causes of mortality and morbidity worldwide. It is known that many modifiable and unchangeable conditions contribute to its etiology. Some modifiable factors include comorbid diseases. The most important risk factor is age (1). However, rheumatologic diseases should also be considered and investigated, especially in strokes that develop at a young age (2). In the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification of ischemic strokes, large vessel atherosclerosis, which are common causes of stroke, strokes of cardiac origin, and strokes that are not caused by lacunar stroke but whose etiology can be determined are classified as TOAST-4. Rheumatologic diseases are the

Peer-Review: Double anonymized - Two External
Plagiarism Checks: Yes - intihal.net
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Selcuk University Press
Genel Tıp Dergisi | e-ISSN: 2602-3741
https://dergipark.org.tr/tr/pub/geneltip
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most important etiologic causes of TOAST-4. Especially young strokes are generally included in this group (3).

The spectrum of rheumatologic diseases is quite broad. Therefore, their neurologic involvement also varies. While some systemic autoimmune diseases affect the peripheral nervous system, others affect the central nervous system more. In particular, systemic lupus erythematosus, rheumatoid arthritis, Takayasu's arteritis, polyarteritis nodosa, systemic vasculitis such as temporal arteritis, and rheumatologic diseases such as psoriatic arthritis and ankylosing spondylitis are known to increase the risk of stroke. Sjögren's syndrome and scleroderma are reported to have no significant adverse effects on stroke (4).

We planned to compare patients who were under rheumatology follow-up or who were diagnosed with rheumatologic disease because of etiologic investigations among patients with a diagnosis of stroke in our clinic with patients with other stroke diagnoses. In conclusion, we aimed to shed light on the differences in the stroke severity, age, and mortality status to help identify patients with rheumatologic diagnosis before stroke development and, if possible, to determine the presence of additional risk factors for stroke development in rheumatologic diagnosis.

Materials and Methods

This study was planned as a retrospective study. Selcuk University Clinical Researches Local Ethics Committee approval was obtained before the study (Approval number: 2020-473). The data of patients who were hospitalized with a diagnosis of stroke in the neurology department of Selcuk University Faculty of Medicine Hospital between 2016 and 2020 were used. Patients over the age of 18 years were included in the study. Patients with subarachnoid hemorrhage, epidural and subdural hematoma, and sinus vein thrombosis were excluded from the study. Patients diagnosed with hemorrhagic stroke, ischemic stroke, transient ischemic attack and hemorrhagic infarction were evaluated. Demographic data such as age, gender, comorbid diseases, stroke types, initial neurologic examination findings, blood on admission, magnetic resonance imaging findings, etiologic evaluations, acute treatment requirements, intensive care unit hospitalization requirements, exitus status, discharge medical treatment, and the number of hospitalization days were recorded for each patient. The comorbid diagnoses of these patients were evaluated, and those who had been diagnosed with rheumatological diseases in the past and those who were diagnosed with rheumatological diseases during the etiological examination were recorded. A comparison with the general stroke group was made.

Statistical analysis

After the data of the patients were entered into the SPSS version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA) program, the distribution analysis of the data was performed using the Shapiro-Wilk test. Categorical variables are expressed as numbers and percentages, continuous variables are expressed as mean±standard deviation if normally distributed, and median (minimum-maximum) if not normally distributed. In independent groups, independent sample t-test or Mann-Whitney U test was used to compare continuous variables and Pearson's chi-square test was used to compare categorical variables. A p-value of 0.05 was considered statistically significant.

Results

The total number of patients included in the study was 2053. Of these patients, 1697 had an ischemic stroke (82.7%), 190 had a transient ischemic attack (9.3%), 146 had a hemorrhagic stroke (7.1%), and 20 had hemorrhagic infarction (1%). The number of patients with rheumatologic diagnoses was 37. Of these patients, 28 (73.7%) had ischemic stroke, 3 (7.9%) had hemorrhagic stroke, 5 (13.2%) had transient ischemic attack, and 1 (2.6%) had hemorrhagic infarction (see Table 1). The mean age of the entire sample was 66.22±14.33 years (19-98), and in terms of gender, there were 1126 male (54.9%) and 924 female (45.1%) patients. In patients diagnosed with rheumatologic disease, the mean age was 51.62±15.88 years and the gender distribution were 21 (56.7%) females and 16 (43.2%) males. The subdiagnosis, gender ratios, and mean age of the rheumatologic patients are shown in Table 2. According to the table, the mean age of patients with rheumatoid arthritis was similar to that of the general sample. In addition, there was a clear female gender predominance in patients with systemic lupus erythematosus and rheumatoid arthritis. There was no significant gender predominance in the other diagnoses.

When the overall sample was evaluated in terms of intensive care hospitalization, it was observed that 865 (42.2%) patients needed intensive care, whereas 1185 (57.8%) patients were followed up only in the ward. When the mortality rates of the patients were analyzed after follow-up, 297 (14.5%) patients died, whereas 1753 (85.5%) patients were discharged. When the same parameters were evaluated for patients with rheumatologic diagnosis, the number of patients requiring intensive care hospitalization was 13 (34.2%), whereas 24 (64.9%) patients were followed up only in the ward. In the mortality evaluation, 5 (13.5%) patients died, whereas 32 (86.4%) patients were discharged from the ward.

According to the TOAST classification, patients diagnosed with ischemic stroke were classified according to their etiology, and their comparison with the entire population is given in Table 3. According to the table, it is noteworthy that the etiology of patients diagnosed with rheumatologic disease is more intense, especially in TOAST-4.

A comparison of the entire stroke population with stroke patients with rheumatologic disease in terms of demographic data, stroke subtypes, intensive care needs, and exitus status is given in Table 4.

According to the table, the mean age of patients with rheumatologic disease was significantly lower than that of the general population (p<0.001). However, no statistically significant difference was found in terms of other parameters.

Table 1: Comparison of groups in terms of stroke subtypes

	Diagnosed without rheumatological disease	Percent	Diagnosed with rheumatological disease	Percent	Entire sample	Percent
Ischemic Stroke	1669	%82.8	28	%75.7	1697	%82.7
Hemorrhagic Stroke	143	%7.1	3	%8.1	146	%7.1
Transient Ischemic Attack	185	%9.2	5	%13.5	190	%9.3
Hemorrhagic Infarct	19	%0.9	1	%2.7	20	%1
Total	2016	%100	37	%100	2053	%100

Table 2: Demographic characteristics of subtypes of rheumatological disease diagnoses

rheumatological diagnosis	number (n)	percent	the average age	female:male
Rheumatoid arthritis	9	%23.7	67.2	8:1
Behcet 's disease	5	%13.2	57.6	2:3
Systemic lupus erythematosus	5	%13.2	45.4	5:0
Granulomatosis with polyangiitis	3	%7.9	55.3	1:2
Familial mediterranean fever	3	%7.9	42.6	1:2
Takayasu's arteritis	3	%7.9	42	1:2
Central nervous system vasculitis	2	%5.3	44.5	0:2
Sjögren's disease	1	%2.6	41	1:0
Anti-phospholipid antibody syndrome	1	%2.6	22	1:0
Ankylosing spondylitis	1	%2.6	37	0:1
Thromboangiitis obliterans	1	%2.6	30	0:1
Polymyositis	1	%2.6	56	0:1
IgG4 related disease	1	%2.6	43	1:0
Unspecified vasculitis	1	%2.6	52	0:1
Total	37	%100	51.62	21:16

Table 3: Etiological evaluation of groups diagnosed with ischemic stroke using TOAST classification

		Patients diagnosed with rheumatological disease	Percent	Entire sample	Percent
TOAST-1	Large vessel atherosclerosis	7	%25	635	%37.4
TOAST-2	Cardioembolic stroke	3	%10.7	275	%16.2
TOAST-3	Small vessel disease or Lacunar stroke	3	%10.7	377	%22.2
TOAST-4	Stroke due to other specified causes	10	%35.7	43	%2.5
TOAST-5	Cryptogenic stroke	5	%17.9	367	%21.6
total		28		1697	

Table 4: Statistical comparison of stroke groups

		Patients diagnosed without rheumatological disease	Patients diagnosed with rheumatological disease	Entire sample	p-value
Age		66.48±14.12	51.62 ±15.88	66.24±14.27	<0.001
Gender	Female	904 (%44.8)	21 (%56.8)	924(%45.1)	p=0.149
	Male	1112 (%55.2)	16 (%43.2)	1128(%54.9)	
Stroke Subtype	Ischemic Stroke	1669 (%82.8)	28 (%75.7)	1697 (%82.7)	p=0.538
	Hemorrhagic Stroke	143 (%7.1)	3 (%8.1)	146 (%7.1)	
	Transient Ischemic Attack	185 (%9.2)	5 (%13.5)	190 (%9.3)	
	Hemorrhagic Infarct	19 (%0.9)	1 (%2.7)	20 (%1)	
Intensive care admission	Yes	852 (%42.3)	13 (%35.1)	865 (%42.2)	p=0.384
	No	1164 (%57.7)	24 (%64.9)	1185 (%57.8)	
Exitus	Yes	292 (%14.5)	5 (%13.5)	297 (%14.5)	p=0.868
	No	1724 (%85.5)	32 (%86.5)	1753 (%85.5)	

Discusion

As stated in the TOAST classification, rheumatologic diagnoses have a defined place in the etiology of stroke (3). Stroke is a vascular disease. In this respect, diseases that cause deterioration in the vascular wall are closely related to stroke. Vascular involvement

also develops in some rheumatologic diseases. Therefore, it would not be an incorrect suggestion to state that some vasculitis increases the risk of stroke.

Vasculitides are classified according to the size of the vessels involved. Temporal arteritis and Takayasu arteritis, which involve large vessels, are present with a more severe neurological picture. Polyarteritis nodosa affects medium-sized arteries. Granulomatosis with polyangiitis involves small vessels. Clinical findings are different from those of large vessel involvement. Bechet's disease can involve any type of vessel. Therefore, it presents a broad clinical picture (4).

Systemic lupus erythematosus (SLE) is a rheumatologic disease in which central nervous system involvement is common. In previous studies, the incidence of stroke in patients with SLE was reported to be between 5% and 18%. However, recent studies have reported that this rate is approximately % 5.6 (6). SLE diagnosis is an independent risk factor for stroke. Antiphospholipid antibody syndrome plays an important role in the etiology of stroke, particularly in young women (7). Antiphospholipid syndrome is frequently seen in individuals with systemic lupus erythematosus and studies have shown that the risk of stroke is 2-fold higher in patients with systemic lupus erythematosus (8).

Rheumatoid arthritis (RA) occurs at a young age and primarily affects the joints. However, other symptoms also occur in different ways at older ages. Cardiovascular involvement and increased risk of stroke are some of these symptoms. Mortality rates after stroke are also reported to be high in these patients (9). In our study population, the mean age of patients with RA was similar to that of the general stroke population. Increasing age, predominance of female gender, and RA diagnosis can be considered significant risk factors for stroke. Therefore, patients with RA diagnosis and healthcare professionals should be aware of stroke-related conditions.

Stroke development is observed in 10%–20% of patients with Takayasu arteritis. It may lead to serious consequences in terms of prognosis, especially because of its involvement in large arteries (10). Vascular imaging, especially digital subtractional angiography (DSA), is very useful in the diagnosis of Takayasu arteritis. In our sample, thrombectomy was performed in the angiography laboratory for the acute treatment of patients admitted under appropriate conditions. All three of our patients with Takayasu's arteritis had no prior diagnosis of Takayasu's arteritis but were suspected and diagnosed during the acute treatment phase.

The most common symptom of temporal arteritis is headache. However, retinal artery occlusion and vision loss may develop in later stages. Because of the involvement of large arteries, there is an increased risk of stroke with the involvement of the aorta and its branches (11).

Polyarteritis nodosa usually involves the periphery and is a cause of neuropathy. However, it also causes ischemic stroke or intracranial hemorrhage less frequently (12).

Behcet's disease, which is quite common, especially in our country, is a multisystemic disease involving vessels. Central nervous system involvement is mostly seen as parenchymal involvement or sinus venous thrombosis. Recent publications indicate that the risk of stroke in patients with Bechet's disease is 2.27 times higher than that in the normal population (13).

Three patients had granulomatosis with polyangiitis. One of them was diagnosed with hemorrhagic stroke. They had a significant rate of 7.9% among patients with rheumatologic disease diagnosis and stroke. In population-based studies, it has been reported that the risk of stroke increases in granulomatosis with polyangiitis, but not to a statistically significant level (14).

Thromboangiitis obliterans is a disease seen in young men and heavy smokers. The etiology of stroke can be found in the literature as single case reports (15). We also had a patient with Buerger's disease in our series.

The risk factors for ischemic stroke and cardiovascular disease are similar. The risk of cardiovascular and cerebrovascular disease was highest at or soon after the diagnosis of anti-neutrophil cytoplasmic antibody-associated vasculitis and cryoglobulinemic vasculitis. Acetylsalicylic acid (ASA), in particular, reduces the risk of stroke in temporal arteritis and Kawasaki disease. In Behcet's disease, immunosuppressive therapies should be preferred over anticoagulants (16).

Our study had some limitations. In particular, in the class considered cryptogenic stroke, there may be patients diagnosed with rheumatologic diseases that have not yet been diagnosed. As the total number of patients followed up in the rheumatology outpatient clinic and their subdiagnosis were not known, the contribution of these diseases in the development of stroke and risk increases could not be evaluated. Our study is a single-center experience. Regional risk factors may affect stroke development. Therefore, studies conducted in different centers may not yield the same results. In addition, some diseases, such as Bechet's disease, may be observed at different rates in other regions. We do not have sufficient data to make a risk assessment.

Conclusion

Some rheumatologic diseases pose a risk of stroke development. In our study, the mortality rate and intensive care hospitalization rate of patients diagnosed with rheumatologic disease were similar to those of the general stroke population. Although female gender predominance was more prominent in some rheumatologic diseases, overall gender ratios were similar in the entire sample.

In addition, it was determined that patients diagnosed with rheumatologic diseases had strokes at a younger age. As is known, having a stroke is itself a risk factor for recurrent stroke. In addition, in patients who have had a stroke at a young age, another risk develops with increasing age. In this respect, we can say that rheumatologic patients have more than one risk factor for stroke. We believe that patients with rheumatologic diseases, which are known to increase the risk of stroke, should be followed up more closely, awareness of stroke should be increased, additional risk factors should be evaluated in terms of prophylaxis if identified, and a multidisciplinary approach should be taken in the axis of rheumatology-neurology.

Ethical Statement: The study protocol was approved by the Selcuk University Clinical Researches Local Ethics Committee (Approval number: 2020-473). Our study was conducted according to the criteria set in the Declaration of Helsinki.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Financial Disclosure: The authors declare that this study received no financial support.

Author Contributions: CO: planning, organization, data collection, writing, and editing. SO: planning, organization, and editing. GO: data collection and editing. All authors contributed to the article and approved the submitted version.

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