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Original Article RHEUMATOLOGY

Rheumatic diseases presenting with young ischemic stroke: Revelations from tertiary center experience

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ABSTRACT

OBJECTIVE: The aim of this study is to determine the frequency and clinical features of diagnosed rheumatological disease in patients who have no previous history of rheumatic disease and are consulted to the rheumatology clinic from other departments to investigate the etiology of early-onset ischemic stroke.

METHODS: Patients aged 18-65, who had not previously been diagnosed with rheumatic disease, had ischemic stroke for the first time, and were consulted to rheumatology clinic to investigate the etiology of the disease, were retrospectively included in the study. Demographics, clinic laboratory, imaging data and the final diagnosis of the patients were obtained from hospital records.

RESULTS: A total of 115 patients who had their first ischemic stroke were identified in the study. 70 of them were detected to have young ischemic stroke. Of these patients, 1 was diagnosed with lupus with secondary antiphospholipid syndrome (APS) and Sjögren's syndrome 1 with lupus and secondary APS, 2 with primary APS, 1 with lupus, 1 with primary Sjögren's syndrome and 1 with granulomatous with polyangiitis.

CONCLUSION: Determining the correct etiological diagnosis of ischemic stroke, especially in young adults, is important in terms of preventing recurrent ischemic attacks. It is important to raise awareness of clinicians in terms of rheumatic diseases and to refer patients to the rheumatology department if deemed necessary.

Keywords: Antiphospholipid syndrome; rheumatic disease; stroke; vasculitis.

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Ischemic stroke is a major health problem that affects more than 15 million patients worldwide every year, resulting in the death of approximately one-third of them and causing sequelae in the remaining survivors [1]. Strokes in adults under the age of 49 are known as "juvenile stroke" or "young stroke" and approximately 10–14% of ischemic strokes occur in this group [2–4]. The impact of stroke on quality of life is more devastating in young adults as the younger population is expected to live with acquired disabilities longer. Considering this, preventing stroke in young adults is a worldwide public health issue.

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Depending on the country, the incidence of ischemic stroke in young adults ranges from 7 to 100 per 100,000. This frequency gradually increases over the age of 35 [1]. The increased frequency of diabetes, hypercholesterolemia, obesity, smoking, alcohol abuse, air pollution, or illicit drug use in young adults are thought to be common culprits in the etiology. In the Helsinki Young Stroke Registry, where ischemic stroke patients between the ages of 15 and 49 were evaluated, the most common causes of ischemic stroke in young people were determined as cardioembolism, cervicocerebral artery dissection, small vessel disease, large artery atherosclerosis and unknown etiology [3].

Rheumatic diseases such as Takayasu's arteritis (TA), Behçet's syndrome (BS), systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome (APS), primary Sjögren's syndrome (pSS), and other systemic vasculitides have also been reported to play a role in the etiology of acute ischemic stroke in young adults [5]. In a considerable number of cases, ischemic stroke may be the first manifestation of the disease and diagnosis could be made by referral to rheumatology in suspected cases.

Determining the etiology of ischemic stroke at a young age is crucial to avoid recurrence since life expectancy is longer in this patient subset. Therefore, awareness regarding a variety of clinical scenarios and referring the patient accordingly have utmost importance. To the best of our knowledge, there is no study evaluating the frequency of rheumatological disease in young adults presenting with ischemic stroke.

The aim of this observational study is to determine the impact of rheumatic conditions in young ischemic stroke by investigating frequency and clinical features in patients who have no previous history of rheumatic disease and were consulted to the rheumatology clinic for investigation of possible rheumatic etiology.

Highlight key points

- Strokes in adults under the age of 49 are known as "juvenile stroke" or "young stroke" and approximately 10–14% of ischemic strokes occur in this group.
- Rheumatic diseases such as Takayasu's arteritis (TA), Behçet's syndrome (BS), systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome (APS), primary Sjögren's syndrome (pSS), and other systemic vasculitides have also been reported to play a role in the etiology of acute ischemic stroke in young adults
- Female gender was more frequent and age was younger. APS was the most common diagnosis, followed by SLE, pSS and GPA.

MATERIALS AND METHODS

This retrospective, observational study was carried out in accordance with the principles of the Declaration of Helsinki, with the approval of the Ankara City Hospital Ethics Committee (date: 17.08.2022, number: E1-22-2832). Patients between ages of 18–65 years, who had not previously been diagnosed with a rheumatic disease, had ischemic stroke for the first time and were consulted to rheumatology clinic for differential diagnosis between January 2020 and August 2022 were retrospectively investigated and included in the study. Patients with a previous diagnosis of rheumatic disease, recurrent or transient ischemic stroke, hemorrhagic stroke, ischemic stroke after trauma, surgery or malignancy, and cerebral vein thrombosis and subarachnoid hemorrhage were excluded from the study.

Demographics, comorbidities, smoking history, family history of stroke and rheumatic diseases, genetic test results, clinical, imaging and laboratory characteristics of all patients were collected from hospital records. Indicators of a rheumatic condition such as arthralgia, arthritis, dactylitis, enthesitis, rash, purpura, skin ulcers, skin thickening, telangiectasis, xerostomia, xeropthalmia, photosensitivity, Raynaud's phenomenon, oral and genital ulcers, history of erythema nodosum, uveitis, episcleritis/scleritis, obstetric complications, psoriasis, inflammatory bowel disease, previous history of thrombosis in any other site, any other related organ involvements and others were recorded. As for laboratory tests, results of antinuclear (ANA) and antineutrophil cytoplasmic antibody (ANCA) immunofluorescence assays, polymerase 3 (PR3) and myeloperoxidase (MPO) ANCA enzyme-linked immunosorbent assay (ELISA) results, rheumatoid factor, anticardiolipin antibody (Immunoglobulin [IG] G/IgM), lupus anticoagulant (LAC) analysis, beta-2 glycoprotein antibody (IgG/IgM), anti-dsDNA ELISA and other extractable nuclear antibody tests, complement (C) 3, 4 levels and urinalysis results were recorded if present. Schirmer's test and minor salivary gland biopsy results requested according to the patients' symptoms were noted. Cranial imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) results were examined.

Statistical Analysis

Statistical analyses were made by using Statistical Package for Social Sciences (SPSS) v22 (IBM Corp., Armonk, NY). Normality of variables was analyzed both

Table 1. Demographics, comorbidities and risk factors for ischemic stroke in patients with and without rheumatic disease

	Patient with a diagnosis of a rheumatic disease (n=7)	Patient without a diagnosis of a rheumatic disease (n=63)
Female, (%)	71.4	46
Age, year, mean±SD	33.14±10.49	37.39±8.87
Risk factors, (%)		
Diabetes mellitus	0	11.1
Hypertension	0	22.2
Hyperlipidemia	14.3	28.6
Coronary artery disease	0	3.2
Trombophilia	0	11.1
Smoking	28.6	28.6
Family history	0	3.2
Recent pregnancy	0	17
Congenital heart disease	14.3	4.8
HbA1c, mean±SD	5.40±0.56	5.69±0.65
LDL, mean±SD	99±39	90±30
HDL, mean±SD	40±7.07	38.30±8.53
Triglyceride, mean±SD	136±76.36	152.10±47.81
High homocystine level, (%)	14.3	94
Low Protein C activity, (%)	0	1.6
Low Protein S activity, (%)	0	9.5
Antithrombin III deficiency, (%)	0	6.5
Active protein C resistance, (%)	0	17.5
Thrombophilia mutations, (%)		
MTHFR heterozygous	0	3
MTHFR homozygous	0	2
PAI	0	0
FV heterozygous	0	1
FXIII heterozygous	0	1
FII	0	0

SD: Standard deviation; HbA1c: Hemoglobin A1C; LDL: Low density lipoprotein; HDL: High density lipoprotein.

Table 2. Autoantibody status of the patients with and without rheumatic disease

	Patient with a diagnosis of a rheumatic disease (n=7)	Patient without a diagnosis of a rheumatic disease (n=63)
Number of patients with at least one autoantibody positivity including ANA and ANCA IFAs (%)	100	57.1
Autoantibody positivity, (%)		
ANA-IFA*	71.4	33.3
Anti dsDNA – ELISA	42.9	0
Anti-Ro/SS-A	28.6	1.6
Anti-La/SS-B	0	0
Anti-Ro52	28.6	8.2
Anti-Ribozomal P	0	1.7
Anti-Histon	0	6.6
Anti nRNP/Sm	14.3	6.7
Anti-Sm	42.9	8.3
Anti-Scl-70	0	1.7
CENP-B	0	1.7
Anti-Jo-1	0	1.7
Anti-Mi-2 (+)	0	3.3
DFS-70 (+)	0	11.7
p ANCA-IFA*	0	4.8
c ANCA-IFA*	14.3	0
MPO ANCA-ELISA	0	0
PR3 ANCA-ELISA	14.3	0
Lupus anticoagulan	28.6	3.2
Beta-2 glycoprotein Ig M	42.9	3.2
Beta-2 glycoprotein Ig G	28.6	1.6
Anti cardiolipin antibody IgM	14.3	0
Anti cardiolipin antibody IgG	28.6	1.6

SD: Standard deviation; ANA:Antinukleer antibody, ANCA: Antineutrophil cytoplasmic antibody; *: 1/100 titer was accepted positive for ANA-IFA, 1/10 titer for ANCA-IFA.

by plots and histograms, and Shapiro-Wilk test. Continuous variables were presented by either medians and interquartile range (IQR) or means with standard deviations (SD). Categorical variables were presented by numbers and percentages.

RESULTS

A total of 115 patients who had their first ischemic stroke were evaluated. 70 (59.8%) of these patients were identified to be under the age of 49, while 45 (38.5%) were over the age of 50. Among patients under the age of 50, 7 patients were diagnosed with a rheumatic disease meeting relevant classification criteria.

Demographic, clinical and laboratory comparison of patients with and without rheumatic disease is shown in Table 1. Patients with a rheumatic condition were younger and more frequently female, yet these discrepancies were not statistically significant. Comorbidities which may increase the risk of ischemic stroke were less frequent in patients with rheumatic diseases, except for

smoking and congenital heart disease. As for laboratory parameters, none of the rheumatic patients had low protein C/S activity, antithrombin III deficiency or active protein C resistance and only single patient had high homocysteine level (Table 1). None of the patients with a rheumatic diagnosis had thrombophilia mutations, on the other hand, in non-rheumatic group 5 patients had MTHFR mutations (3 heterozygous, 2 homozygous), 1 FV and 1 FXIII mutations (both heterozygous).

Autoantibody profiles of both groups are presented in Table 2. All patients in rheumatic group had at least one autoantibody positivity with ANA-IFA being the most common (71.4%) and followed by ds-DNA ELISA (42.9%), anti-Sm (42.9%), anti-beta2 glycoprotein IgM (42.9%). In the non-rheumatic group, 57.1% of the patients had at least one autoantibody positivity with ANA-IFA being the most common (33.3%), followed by anti-DFS70 (11.7%), anti-Sm (8.3%), anti-Ro52 (8.2%).

The diagnosis of rheumatic patients with young stroke according to relevant classification were as follows: 1 with SLE and secondary APS and secondary SjS, 1 with SLE and secondary APS, 2 with primary APS, 1 with SLE, 1 with pSS and 1 with granulomatosis with polyangiitis (GPA). Table 3 shows detailed demographic, clinical, and laboratory features of young ischemic stroke patients. Three patients had another concomitant risk factor for ischemic stroke. One had congenital heart disease, one was active smoker, and one was active smoker and had hyperlipidemia.

DISCUSSION

Our results demonstrated that among 70 young ischemic strokes without a known rheumatic condition who were referred to rheumatology clinic for differential diagnosis, 10% were diagnosed with a rheumatic disease meeting relevant classification criteria. Female gender was more frequent and age was younger. APS was the most common diagnosis, followed by SLE, pSS and GPA. No thrombophilic mutations were present in these patients. Three of them had additional risk factors for ischemic stroke.

Rheumatologic diseases may cause young ischemic stroke via various mechanisms. Thrombotic events may be a disease manifestation in some conditions; furthermore, factors such as treatment agents, comorbidities, cardiac involvement may contribute to the overall burden. The frequency varies depending on the underlying rheumatological disease. However, the prevalence of rheumatological disease diagnosed for the first time with stroke is unknown. There are no studies in the literature; only case reports have been presented [1, 6–9]. In our cohort, 7 young adult patients presented with ischemic stroke before the diagnosis of rheumatic disease and this frequency was calculated as 10%. However, this result should be interpreted with caution since these patients were referred to rheumatology clinic possibly due to suspicion of a rheumatic condition, for example antibody positivity or a symptom/sign, causing selection bias. Small sample size was another setback for illuminating true incidence.

Antiphospholipid syndrome, considered the most common acquired thrombophilia, is an autoimmune condition characterized by the occurrence of thrombotic events and/or pregnancy comorbidities in individuals positive for antiphospholipid antibodies (aPL). Thrombotic events in APS can have an impact on both the venous and arterial systems [10]. In arterial incidents, the central nervous system is the most commonly impacted organ [11]. Cerebrovascular disease is the most common cause of neurological symptoms in patients with APS, and ischemic stroke or transient ischemic attack may be the first symptom in almost 30% of adults with APS [12]. Ischemic stroke involving the middle cerebral artery territory is the main site of neurological involvement associated with APS [11]. It has been reported that positivity of aPL in patients under the age of 50 increases the frequency of cerebrovascular thrombotic events by 5 times [13]. The prevalence of aPL in young persons under 50 years of age has been reported to be 17.2% (2-56%) when all patients with cerebral ischemia episodes are considered [13]. In the Euro-Phospholipid cohort, the prevalence of stroke in APS patients was reported as 19.8% [12]. On the other hand, the frequency of positive aPLs in stroke patients varies between 7% and 15%, and there is an age-dependent relationship between aPL positivity and stroke. The average age of stroke patients with aPL positivity is younger than other stroke patients [14]. In our patient group, primary and/or secondary APS was the most common diagnosis.

The mechanisms of cerebral involvement in APS are not fully understood, but more than one mechanism has been suggested. These include annexin shield disruption, allowing antiphospholipid antibodies to disrupt the endothelium, suppression of the protein C pathway, platelet activation, broad production of adhesion molecules, and endothelial tissue factor [15, 16]. Risk factors for each clinical phenotype of neurological involvement

TABLE 3. Demographic, clinical and laboratory characteristics of young stroke patients

	Patient-1	Patient-2	Patient-3	Patient-4	Patient-5	Patient-6	Patient-7
Age, years	33	23	20	46	29	28	47
Gender	Female	Female	Female	Male	Female	Female	Male
Risk factors	Congenital heart disease, hyperhomocysteinemia	No	No	Smoking	No	No	Smoking Hyperlipidemia
Positive laboratory findings	PR3ANCA:103 C-ANCA-IFA: 1/32	ANA: 1/1000 (granular) SSA: +3 Ro-52: +1	ANA: 1/1000 (homojen) dsDNA-ELISA: 304 Sm: +2	ANA: 1/1000 (homojen) SSA: +2 Ro-52: +1 SM: +1 SM/RNP: +1 dsDNA-ELISA β2-GP IgM: 200 ACA IgM: 105 Hypocomplementemia	ANA: 1/320, (granular) dsDNA-ELISA: 94 LAC: 73 ACA IgG: 34 Hypocomplementemia Proteinuria Leukopenia Thrombocytopenia	ANA: 1/320, (granular) SM: +1 LAC: 60 ACA IgG: 74 β2-GP IgM: 93 β2-GP IgG: 60 Leukopenia thrombocytopenia	β2-GP IgM: 98 β2-GP IgG: 45
Systemic findings	Nasal ulcers Polyneuropathy	Xeropthalmia Xserostomia Arthralgia Shirmer's bilateral<5 mm Salivary gland bx: CM grade 3	Malar rash, Arthralgia Nasal ulcer	Arthralgia Photosensitivity Xserostomia Alopecia Shirmer's bilateral <5 mm Salivary gland bx: CM grade 3	Miscarriage Malar rash	Miscarriage Arthralgia Xserostomia	Arthralgia Fever
Diagnosis	GPA	Sjögren	SLE	SLE+APS+Sjögren	SLE+APS	APS	APS
Cranial imaging	Right paramedain region of the mesencephalon ischemia	Medulla oblongata posterior ischemia	Right cerebellum ischemia	Right centrum semiovale and internal capsule ischemia	Right occipital lobe, centrum semiovale, right internal capsule ischemia	Right cerebellum, both thalami, mesencephalon right pons ischemia	Left temporoparietal area ischemia

ANA: Antinukleer antibody; ANCA: Antineutrophil cytoplasmic antibody; β2-GP IgM: Beta-2 glikoprotein IgM; β2-GP IgG: Beta-2 glikoprotein IgG; ACA IgM: Anticardiolipin IgM; ACA IgG: Anticardiolipin IgG; LAC: Lupus anticoagulant; GPA: Granulomatous polyangiitis; SLE: Systemic lupus erythematosus; APS: Anti phospholipid syndrome.

have been proposed but are not yet fully understood. A study found that central nervous system symptoms are connected with a specific aPL profile with concomitant positivity for IgG antibodies against prothrombin and phosphatidylglycerol by assessing the existence of 20 different aPLs and their interaction with different symptoms in APS [17]. Previous studies have also suggested a correlation between cognitive deficit and higher aPL titers [18]. In this study, 2 of the patients with early-onset ischemic stroke who had not previously been diagnosed with rheumatic disease were diagnosed with APS secondary to SLE, and 2 were diagnosed with primary APS. While all patients had middle cerebral artery involvement, one patient also had posterior cerebral artery involvement and one patient had vertebrobasilar system involvement. Therefore, especially in patients presenting with young-onset cerebrovascular disease, APS-related symptoms such as history of miscarriage, early fetal loss, and previous thrombotic events should be questioned and aPL tests should be requested.

Demonstrating aPL positivity is crucial for identifying APL patients. Levels of titers are related with the risk of thrombotic events. However, positivity of these autoantibodies should be persistent for at least 12 weeks for classification in Sapporo criteria [10], and in the recent classification criteria set [19] it has a weight of 5 points. In our study, in non-rheumatic group, 3.2% of the patients had lupus anticoagulant positivity, 3.2% had beta-2 glycoprotein IgM positivity, 1.6% had beta-2 glycoprotein IgG and 1.6% had anticardiolipin IgG positivity. None of these subjects met either criteria for APS mostly due to impersistent aPL positivity.

Cerebrovascular disease accompanying SLE is another point of interest. Although the pathogenesis underlying the increased risk of stroke in SLE patients is the subject of ongoing research, increased atherosclerosis likely plays a role. Factors such as the increased frequency of comorbidities in SLE patients and exposure to drugs such as proinflammatory cytokines, prothrombotic antiphospholipid antibodies, hyperhomocysteinemia, renal dysfunction, embolism from Libman-Sacks endocarditis and glucocorticoids increase the risk of ischemic stroke in these patients [20–22]. Furthermore, the concept of 'seronegative APS' may also be a matter yet to be fully elucidated. Studies have shown a higher relative risk of stroke in younger patients with SLE compared to age-matched controls, and a meta-analysis found that SLE was associated with an increased risk of ischemic stroke, with a pooled RR of 2.18 [23]. In our cohort, 3 SLE patients presented for the first time with ischemic stroke and APS accompanied two of these. As a result, SLE should come to mind in young stroke patients with or without APS.

The prevalence of central nervous system involvement in primary Sjögren's syndrome ranges from 2% to 60% [24, 25]. However, focal neurological stroke-like condition is very rare. Postulated pathogenic mechanisms for these conditions include immune-mediated vasculopathy, demyelination, or small vessel vasculitis. The presence of anti-SS-A/Ro antibodies, accompanying lung involvement, low C4 complement level and long disease duration increase the risk of central nervous system (CNS) involvement [26]. Additionally, those with anti-SS-A/Ro antibodies were more likely to have more severe and widespread CNS disease [27]. A series of 37 young women with pSS reported evidence of subclinical increased atherosclerosis, with a higher prevalence of carotid intima-media thickening in these patients than in controls [28]. However, in a cohort study involving more than 4000 pSS patients, no increase in the relative risk of ischemic stroke was found when compared to age-, gender- and comorbidity-matched controls [29]. Although rare, pSS cases presenting with ischemic stroke have been reported in the literature before. The case had low complement C4 levels as well as strong positive anti-SSA antibodies and strong positive IgG anti-cardiolipin antibodies and IgG anti-beta2 glycoprotein antibodies. In the case reported in this article, strong positive ANA and anti-SSA antibodies and positive Schirmer's test and minor salivary gland biopsy were detected [9]. Similarly, our case had strong positive ANA and SSA antibodies, positive Schirmer's test and positive salivary gland biopsy. In the etiology of juvenile stroke, serological examination for pSS and, when deemed necessary, investigation for xerolpthalmia and xerostomia should be performed.

Granulomatosis with polyangiitis is a type of small artery necrotizing vasculitis that presents with a variety of organ manifestations. Although the nasopharynx, lungs, and kidneys are the most typically and severely afflicted organs, neuropathies related to peripheral and central nervous system involvement constitute additional consequence. Ischemic stroke is a rare event and usually occurs in the acute phase of untreated GPA. In a 10-year retrospective analysis, the incidence of ischemic stroke in GPA was 11%, four times that of the general population [30]. Increased atherosclerosis has been an emerging pathogenic complication of GPA in recent years. Increased cytokine production, particularly T-helper-17

and T-helper-1, as well as lipid accumulation leading to arterial inflammation, have been linked to atherosclerosis in studies [31, 32]. Additionally, increased carotid intima-media thickness is one of the causes of ischemic stroke in these patients [33]. Previously, GPA cases with lateral medullary stroke with high C-ANCA, infarction in the paramedian pons due to basilar artery occlusion, and occlusion in the left middle carotid artery were reported in the literature [34–36]. In the patient we identified, a young female patient who presented with ischemia in the right paramedian region of the mesencephalon no severe organ-threatening GPA manifestation was present.

The study examines a small patient group and covers a single center. Due to the small number of patients, it is not possible to determine the frequency of young ischemic stroke in rheumatological diseases. Furthermore, selection bias could not be avoided due to retrospective design of the study. Finally, patients were evaluated at the time of the stroke, prospective follow-up of in patients with positive autoantibodies and without rheumatic diagnosis would have been contributory to find out whether new rheumatic manifestations occurred in this group.

Conclusion

In conclusion, determining the correct etiological diagnosis of ischemic stroke, especially in young adults, is important in terms of preventing recurrent ischemic attacks and providing the correct treatment. Therefore, in the approach to ischemic stroke, it is important to raise awareness of clinicians in terms of rheumatic diseases, to conduct systemic questioning, and to refer patients to the rheumatology department if deemed necessary. Larger and prospective studies are mandatory to fully elucidate this issue.

Ethics Committee Approval: The Ankara City Hospital Clinical Research Ethics Committee granted approval for this study (date: 17.08.2022, number: E1-22-2832).

Authorship Contributions: Concept – HEK, SCG; Design – EA; Supervision – SE, BA; Materials – HEK; Data collection and/or processing – HEK; Analysis and/or interpretation – YM; Literature review – PAD, KO, EKE; Writing – HB, RKU, HEK; Critical review – OK, SE, AO.

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