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ORIGINAL ARTICLE

Comorbidity of Stroke in sample of Egyptian Patients with Autoimmune Disease

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Abstract

Background: ***Autoimmune diseases can increase the risk of stroke and are associated with stroke-related disability.***

Aim and objectives: ***To look into the radiographic, laboratory, and clinical characteristics of people who have autoimmune diseases that are exacerbated by stroke.***

Patients and methods: ***Seven06 patients with acute ischemic stroke were included in our observational prospective cohort study; these patients were divided into two groups: 601 patients had no autoimmune illness, and 105 patients had an autoimmune condition.***

Results: ***Among all participants, 27 patients (3.8%) were rheumatoid arthritis (RA), 34 (4.8%) systemic lupus erythematosus(SLE), 23 (3.3%) Behçet disease, 14 (2%) anti-phospholipid syndrome (APS) and 6 (1%) other autoimmune diseases while 601 patients (85.1%) have no autoimmune disease. There were statistically significant differences among studied groups regarding age, sex, stroke onset, diabetes mellitus (DM), hypertension (HTN), ischemic heart disease (IHD), dyslipidemia, and smoking. Patients with the autoimmune disease had frequent small vessel disease, cerebral venous thrombosis (CVT), higher (NIHSS), and higher modified Rankin scale (mRS) compared to the non-autoimmune patients. The patients with atrial fibrillation (AF) were 2.6 times more likely to have a disability compared to those without AF. Additionally, male patients and patients with higher baseline NIHSS were at higher risk of stroke-related disability.***

Conclusion: ***Particularly in young female patients, autoimmune illness is a significant cause of stroke and is frequently linked to concomitant conditions, including DM, HTN, and cardiovascular diseases with more frequent associated small vessel disease, CVT, higher NIHSS, and higher mRS compared to the non-autoimmune patients.***

Keywords: Autoimmune diseases; Stroke; Comorbidities; SLE; Rheumatoid Arthritis

1. Introduction

Stroke is a significant contributor to both disability and death, and it carries a substantial burden of disability-adjusted life years (DALYs).[1] The etiology of ischemic stroke is typically challenging to ascertain, with approximately 25% of patients exhibiting no identifiable cause following a routine diagnostic evaluation.[2,3] One of the causes of this is autoimmune illnesses. Individuals diagnosed with autoimmune disorders such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) have a higher likelihood of experiencing a stroke compared to the general population. However, there is a scarcity of studies that have specifically examined the occurrence of acute ischemic stroke in individuals with autoimmune diseases. It is imperative to identify the clinical characteristics and stroke mechanisms in these patients in order to promptly diagnose the underlying causes, administer precise treatment, and develop effective preventative efforts.[4]

The objective of this study is to examine the clinical, biochemical, and radiological characteristics of individuals with autoimmune illness who have experienced a stroke.

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2. Patients and methods

We conducted a prospective cohort study, observing and collecting data from 706 patients who were clinically and radiologically diagnosed with acute cerebrovascular ischemic stroke. These patients were admitted to the emergency department and stroke unit of Al-Azhar University Hospitals for two years, from October 2021 to October 2023.

We included all patients with evidence of acute ischemic cerebrovascular stroke.

We excluded patients with hereditary blood diseases, coagulopathy, stroke mimic (subdural hematoma, infection, hyperglycemia, hypoglycemia, Todd's paralysis, brain tumor...), and intracranial hemorrhage.

Every patient underwent a comprehensive medical and neurological assessment, including a thorough examination and review of their medical history. The patients were categorized into two groups: one consisting of 601 individuals with non-autoimmune disease and the other consisting of 105 individuals with autoimmune disease. Individuals suffering from Systemic Lupus Erythematosus (SLE) were identified based on the 2019 EULAR/ACR classification criteria for SLE, and the severity of the disease was assessed using the SLE Disease Activity Index-2K (SLEDAI-2K).[5] The 2020 ACR-EULAR for Rheumatoid Arthritis was used to diagnose patients with RA, and the DAS28-ESR was used to gauge disease activity.[6] A Behçet's Disease Activity Measure was used to quantify disease activity in patients with Behçet disease, and revised ICBD criteria were used for diagnosis. Form for Current Activity.[7] Sapporo criteria were used to diagnose patients with (APS).[8]

Laboratory assessment included routine laboratory investigations and Basic immune profile (ESR et al., anti-DNA, rheumatoid factor, ANCA, anti-phospholipid Ab, lupus anticoagulant, and other investigation specific for each disease). Brain CT was done as an initial step to exclude intracerebral hemorrhage. Brain MRI stroke protocol, Echocardiography, and carotid and vertebra-basilar duplex were done for all patients, while CT Angiogram of the neck and cerebral blood vessels and digital subtraction angiogram (DSA) if needed.

The etiological classification of stroke was determined using (TOAST) classification.[9] At admission and discharge, the severity of the stroke was measured using the National Institute of Health Stroke Scale Score (NIHSS). Upon discharge, the Modified Rankin Scale (mRS) was used to measure the severity of the stroke.

The Al-Azhar Faculty of Medicine's Ethics Committee gave its approval to this work. Prior to their involvement in this research, patients or their families provided us with written informed consent.

STATISTICAL ANALYSIS

The data was analyzed using Microsoft Office Excel 2016, the Med CalC program software version 19.1, and the SPSS (Statistical Package for the Social Science) program version 25.0 (IBM Inc., Chicago, USA).

For numerical parametric data, descriptive statistics were calculated as mean ± SD (standard deviation) and the minimum and maximum of the range; for numerical nonparametric data, they were calculated as median and the first and third interquartile range; and for categorical data, they were calculated as number and percentage.

For quantitative variables, inferential analyses were performed using the Mann-Whitney U in the case of two independent groups with nonparametric data and the independent t-test in the case of two separate groups with parametric data. For qualitative data, inferential analyses were performed using the independent group's Chi-square test. P values less than 0.05 were considered significant, with a value of 0.05 indicating non-significantity. A statistical indicator of the likelihood that study outcomes could have happened by accident is the p-value.

3. Results

Table 1. Baseline data comparisons between the study groups.

		FREQUENCY	PERCENT
STUDY GROUPS	Non-autoimmune disease	601	85.1
	Autoimmune disease	105	14.9
TYPES OF AUTOIMMUNE DISEASES	APS	14	2
	Behçet	23	3.3
	RA	27	3.8
	SLE	34	4.8
	Other Autoimmune diseases	6	1

Among all participants, 27 patients (3.8%) were RA, 34 (4.8%) were SLE, 23 (3.3%) were Behçet disease, 14 (2%) were APS and 7 (1%) were primary vasculitis while 601 patients (85.1%) have no autoimmune disease.

Table 2. Comparison of age and stroke onset in both study groups.

	NON AUTOIMMUNE (601)		AUTOIMMUNE DISEASE (105)		P-VALUE
	Mean/median	SD/IQR	Mean/median	SD/IQR	
AGE	61.77	8.25	37.33	8.60	<0.001*
ONSET OF STROKE	7	3-48	12	5-48	0.003*

SD; standard deviation, IQR; interquartile range. Mann-Whitney test was used for the stroke onset comparison, while independent t-test was used for age comparison at 0.05 level of significance.

There was a statistically significant differences regarding age and stroke onset (p< 0.05) among studied groups.

Table 3. Comparison of comorbidities in both study groups.

COMORBIDITIES		NON AUTOIMMUNE (601)		AUTOIMMUNE DISEASE (105)		P-VALUE
		Number	%	Number	%	
SEX	Female	260	43.26	66	62.86	<0.001*
	Male	341	56.74	39	37.14	
DM	No	290	48.25	91	86.67	<0.001*
	Yes	311	51.75	14	13.33	
HYPERTENSION	No	180	29.95	84	80.00	<0.001*
	Yes	421	70.05	21	20.00	
IHD	No	425	70.72	98	93.33	<0.001*
	Yes	176	29.28	7	6.67	
AF	No	488	81.20	93	88.57	0.068
	Yes	113	18.80	12	11.43	
DYSLIPIDEMIA	No	221	36.77	68	64.76	<0.001*
	Yes	380	63.23	37	35.24	
SMOKING	No	369	61.40	83	79.05	<0.001*
	Yes	232	38.60	22	20.95	
PREVIOUS STROKE	No	436	72.55	98	93.33	<0.001*
	Yes	165	27.45	7	6.67	

Chi-Square test/Fisher exact test was used for the above comparisons. *: significant p-value at 0.05 level.

There were significant differences between both groups as regarding sex, DM, HTN, IHD, dyslipidemia, smoking, and stroke history (p < 0.05). However, the distribution of AF did not show significant difference between the groups.

Table 4 Comparison of TOAST classification in both study groups.

OUTCOMES		NON AUTOIMMUNE (601)		AUTOIMMUNE DISEASE (105)		P-VALUE
		Number	%	Number	%	
TOAST CLASSIFICATION	Cardio embolic	156	25.96	20	19.05	<0.001*
	Cryptogenic	95	15.8	3	2.86	
	CVST	7	1.16	16	15.24	
	Large artery atherosclerosis	169	28.12	27	25.71	
	Small vessel disease	176	29.28	39	37.14	

Chi-Square test was used for the above comparisons. *: significant p-value at 0.05 level.

There was significant difference in TOAST classification findings between the study groups, whereas patients with autoimmune disease had more frequent small vessel disease, CVT, compared to the non-autoimmune patients.

Table 5. Comparison of NIHSS in both study groups

OUTCOMES	NON AUTOIMMUNE (601)		AUTOIMMUNE DISEASE (105)		P-VALUE
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
NIHSS	10.46 ± 4.93	9 (7-13)	11.23 ±4.71	11 (8-14)	0.1

SD; standard deviation, IQR; interquartile range. Mann-Whitney test was used for the above comparison at 0.05 level of significance.

. Table 6. Comparison of mRS in both study groups.

OUTCOMES		NON AUTOIMMUNE (601)		AUTOIMMUNE DISEASE (105)		P-VALUE
		Number	%	Number	%	
MRS	1	55	9.15	7	6.67	<0.019*
	2	178	29.62	20	19.05	
	3	164	27.29	35	33.33	
	4	115	19.13	26	24.76	
	5	44	7.32	14	13.33	
	6	45	7.49	3	2.86	
MRS	0-2	233	38.77	27	25.71	0.011*
	3-6	368	61.23	78	74.29	

Chi-Square test was used for the above comparisons. *: significant p-value at 0.05 level.

Table 7. Binary logistic regression of stroke-related

INDEPENDENT VARIABLES	BETA	S.E.	P-VALUE	ADJ. OR
AUTOIMMUNE DISEASE	0.629	0.441	0.154	1.875
AGE	0.002	0.013	0.896	1.002
MALE SEX	0.638	0.231	0.006*	1.892
DIABETES	0.367	0.212	0.083	1.444
HYPERTENSION	-0.293	0.228	0.199	0.746
IHD	0.361	0.241	0.134	1.435
AF	0.975	0.281	0.001*	2.652
DYSLIPIDEMIA	0.307	0.209	0.141	1.359
SMOKING	-0.354	0.238	0.138	0.702
PREV CVS	-0.139	0.249	0.577	0.871
NIHSS (BASELINE)	0.36	0.033	<0.001*	1.433
ONSET OF STROKE	0	0.002	0.918	1
INTERVENTION WITH RTPA	0.068	0.214	0.75	1.071
INTERVENTION WITH THROMBECTOMY	-1.53	0.621	0.014*	0.217
CONSTANT	-3.644	0.874	0	0.026

Beta; regression coefficient, SE; standard error, OR; odds ratio, *; significant p-value at 0.05 level. Omnibus Tests of Model Coefficients has a Chi-square value of 265.87 (p < 0.001). Hosmer and Lemeshow Test has a Chi-square value of 27.12 (p < 0.001). Nagelkerke R Square = 0.438

disability (mRS > 2) among the study patients.

The incidence of stroke-related disability was higher in autoimmune disease patients than in non-autoimmune patients, although the difference was not statistically significant (adjusted OR = 1.875, p = 0.154). On the other hand, compared to individuals without AF, those with AF had a 2.6-fold higher likelihood of being disabled (adjusted OR = 2.65). Furthermore, patients who were male and had a higher baseline NIHSS were more likely to experience disability from a stroke.

4. Discussion

Stroke is a significant contributor to both disability and death, and it carries a substantial burden of disability-adjusted life years (DALYs).[1] Autoimmune disease is an uncommon factor that can lead to stroke, and there is a limited number of comprehensive studies available to assess the occurrence of autoimmune disease in individuals with numerous acute ischemic strokes.[4]

The objective of this study was to examine the clinical, biochemical, and radiological characteristics of individuals with autoimmune illness who experienced stroke as a complication.

Among all participants in our study, 27 patients (3.8%) had RA, 34 (4.8%) had SLE, 23 (3.3%) had Behçet disease, 14 (2%) had APS, and 7 (1%) had primary vasculitis, while 601 patients (85.1%) had no autoimmune disease.

As regards demographic data, there were significant differences between both groups regarding stroke onset, age, sex, DM, HTN, IHD, dyslipidemia, smoking, and stroke history (p < 0.05). However, the distribution of AF did not show a significant difference between the groups.

In our study, 62.86 % of patients with autoimmune diseases were female. This comes in agreement with most of the research, as most autoimmune diseases are common in females.[10] The causes of this gender bias are not yet completely comprehended, although various possibilities have been put up. One concept is that sex hormones contribute to the development of autoimmune illnesses. Another conjecture posits that the presence of two copies of the X chromosome in women and just one copy in males may play a role in the gender disparity observed in autoimmune diseases.[10]

On the other hand, 56.74% of patients with non-autoimmune diseases were male. This comes in agreement with most research, and this is because men are at a higher risk for stroke compared to women due to several factors, including a higher incidence of high blood pressure, smoking, alcohol consumption, obstructive sleep apnea, heart disease, diabetes, and high cholesterol.[11]

The average age of patients without autoimmune diseases was 61.77 ± 8.25. Consistent with numerous research, it has been found that advancing age is a notable risk factor for stroke. The likelihood of experiencing a stroke increases double every decade after reaching the age of 55. Furthermore, around 75% of all strokes occur in individuals who are 65 years or older.[12]

The average age of patients with autoimmune diseases was 37.3 ± 8.60. The age at which autoimmune disorders first appear might vary significantly depending on the specific disease. Moreover, many autoimmune diseases tend to emerge more frequently during the latter half of life, when there is a reduction in immune function.[13]

Regarding diabetic mellitus (DM), there were statistically significant variations between both groups (p < 0.05). Diabetes mellitus (DM) is frequently seen alongside stroke in patients, making it a common comorbidity. DM is also a standalone risk factor for ischemic stroke, with individuals having DM experiencing a higher relative risk ranging from 1.8 to over 6.0. A comprehensive study conducted on a substantial group of stroke patients who were admitted to the hospital revealed a significant correlation between diabetes mellitus (DM) and an increased likelihood of experiencing sequelae, long-term mortality, and recurrence.[14]

Regarding hypertension, there were notable distinctions seen between the groups (p < 0.05). It has been found that autoimmune illnesses, such

as systemic lupus erythematosus (SLE), are connected to a higher occurrence of hypertension. Multiple research has emphasized the connection between autoimmunity and hypertension, underscoring the influence of genetic, environmental, hormonal, and metabolic variables in developing long-lasting inflammation and cardiovascular problems.[15]

Regarding dyslipidemia, there were significant differences observed between both groups ($p < 0.05$). This can be attributed to the fact that autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), are linked to an increased risk of abnormal lipid profile, which in turn contributes to the development of atherosclerosis. The inflammatory state associated with autoimmune diseases further accelerates the formation of arterial plaques. This occurs through direct effects on the arterial wall as well as inflammation-mediated changes in the lipid profile.[16]

Regarding the TOAST categorization, there was a statistically significant disparity between the two groups. Individuals with autoimmune disease had a higher occurrence of small vessel disease and CVT compared to non-autoimmune individuals. Small vessel disease is highly prevalent, representing around 20% of all strokes, and significantly amplifies the likelihood of further strokes by over 50%. The symptoms encompass cognitive and balance impairment as well as dementia.[17-18] The development of CVT (cerebral venous thrombosis) is caused by a combination of causes, including increased blood clotting and damage to the blood vessel walls.[19,20]

As regards stroke disability and outcome, the baseline (NIHSS) score is a strong predictor of stroke-related disability. Research has consistently demonstrated the predictive power of the NIHSS score in assessing the severity of stroke and its impact on patient outcomes.21 In the context of this mRS, there was a statistically significant difference between both groups. Patients with autoimmune illness exhibited a higher incidence of moderate to severe impairment. Higher mRS in autoimmune diseases may be explained by the impairment of function and the disability caused by the autoimmune disease itself.22 While the mRS and NIHSS have been extensively used in stroke trials and other neurologic conditions, their direct application and findings in the context of autoimmune disease-related stroke may require further specific research and documentation; this would benefit from additional focused studies to provide comprehensive insights into its use and implications in this particular domain.[21]

In our analysis, the prevalence of stroke-related impairment was higher among patients with autoimmune illness compared to those without autoimmune disease, but this difference was not statistically significant. Nevertheless, individuals diagnosed with AF had a 2.6-fold higher likelihood of experiencing a handicap in comparison to those without AF. Furthermore, it was observed that male patients and patients with a higher baseline NIHSS score had an increased susceptibility to stroke-related disability. Multiple studies have documented a higher degree of disability in strokes linked with atrial fibrillation (AF) as compared to strokes not associated with AF.[23] Individuals who have experienced a stroke linked with atrial fibrillation (AF) exhibit more severe neurological deficits, increased disability, elevated death rates, and a higher likelihood of experiencing further strokes. Studies such as the Framingham research have shown that atrial fibrillation (AF) is related to a fivefold increase in the risk of stroke.[24]

Even though this study's results are encouraging, there were several limitations. First, the study is a single-center cohort with a moderate sample size. The second limitation was the short follow-up period, which limited the capacity to identify the long-term effects of stroke in patients with autoimmune diseases. To address the shortcomings of the current study, more long-term follow-up protocols and randomized clinical trials with sizable sample sizes should be implemented.

4. Conclusion

Particularly in young female patients, autoimmune diseases are a significant cause of stroke and are frequently linked to concomitant conditions, including DM, HTN, and cardiovascular diseases with more frequent associated small vessel disease, CVT, higher NIHSS, and higher mRS compared to the non-autoimmune patients. These findings emphasize the need for effective management of autoimmune disease stroke patients to improve outcomes.

Disclosure

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