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Silent Brain Infarction; Risk Factors and Effect on Outcome of Acute Ischemic Stroke

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ABSTRACT

Background: Stroke is a major contributor to disability and the second a major contributor of death globally. Silent brain infarction is an example of a subclinical risk factor for stroke that, if identified, might lead to earlier and more effective preventative measures.

The aim of the work: To detect risk factors of silent brain infarctions [SBI] and its effect on outcome of first ever acute ischemic stroke.

Patients and Methods: In a prospective research, 76 cases diagnosed clinically and radiologically as first ever ischemic stroke and admitted to emergency department and stroke unit of Al-Azhar University hospitals were enlisted beginning in December 2022 to May 2023. They were categorized into two groups: patients with SBIs [38 patients] and patients without SBIs [38 patients].

Results: We assessed 76 cases presented with first ever acute ischemic stroke with and without SBI. Age was significantly higher in cases with SBI contrasted with cases without SBI with male to female ratio 1: 1.5 without significant difference. There was a significant variance among both groups regarding HTN, DM, ischemic heart diseases, and the degree of stenosis at right, left carotid and vertebrobasilar arteries, the size of infarction and the assessment of cognitive function using Mental State Examination [MSE] and Montreal Cognitive Assessment Scale [MOCA] after 3 months. The Modified Rankin score after 3 months from onset was significantly different between both groups and all cases with moderate to severe and severe disability were having SBI. And there was a significant variance regarding the baseline & after one-week National Institute of Health stroke scale [NIHSS].

Conclusion: Hypertension was identified as the most important risk factor of SBI. SBI affects cognitive function and affected patients have a higher probability of developing vascular dementia in addition to Sever long term disability and functional outcome.

Keywords: Silent brain infarction; Acute ischemic stroke; Risk factors.

INTRODUCTION

Although stroke is a key contributing factor in disability, one such potential risk factors, silent brain infarctions [SBI] which are focal or multi-focal and presumed to be ischemic in nature in cases without a history of an obvious neurological deficit related to these lesions [1].

Moreover, there are no clear data about the incidence and prevalence of SBI, and our knowledge of its risk factors remains controversial and limited.

This research intended to demonstrate the risk factors for SBI and its potential effect on the outcome of acute ischemic stroke.

PATIENTS AND METHODS

The current study was a prospective research, was done in Al-Azhar University hospitals from December 2022 to the end of May 2023. We included 76 patients aged above 18 years with the first clinically evident ischemic stroke. We excluded patients with either previous ischemic stroke and/or transient ischemic attack, previous intracranial hemorrhage, traumatic brain injury, cranial interventions/surgery, or neuroinflammatory diseases. Cases were categorized into two groups: group 1[cases] those with SBI [38 patients] and group 2 [controls] without SBI [38 patients].

The subsequent data was gathered: complete general and neurological examination, detailed medical and neurological history, stroke severity assessment at admission utilizing the NIHSS [0 = no stroke, 1 to 4 = minor stroke, 5 to 15 = moderate stroke, 16 to 20 = moderate to severe stroke, 21 to 42 = severe stroke] at admission [2], and laboratory tests [CBC, cholesterol, TG, LDL, HDL, serum uric acid, and RBS]. All patients received extensive evaluation including electrocardiography [ECG], Echocardiography and vascular imaging of intracranial and extracranial cerebral vessels. Both cognition and disability outcome of stroke were assessed after three months, utilizing Mini-MSE [MMSE], MOCA [The total possible score is 30 points; a score of 26 or above is regarded normal] [3] and modified Rankin scale [MRS] [0= no symptoms, 1 = no disability, 2 = slight disability, 3 = moderate disability, 4 = can't walk without support, 5 = bedridden 6 = death] for neurologic disability respectively [4].

This research was carried out in accordance with the declarations of Helsinki and received clearance from an institutional review board through the ethical section of the Faculty of Medicine at Al-Azhar University.

Statistical analysis: In order to determine the statistical significance, the program SPSS [Statistical Package for the Social Science] version 25.0 [IBM Inc., Chicago, USA] and Microsoft Office Excel 2016 were utilized. In order to verify that the data followed a normal distribution, we employed the Kolmogorov–Smirnov test. For each of the analyzed parameters and each of the groups that were investigated, descriptive statistics were calculated. The quantitative data were expressed by percentages and numbers. Quantitative parametric data were expressed by their mean together with their standard deviation. The Chi square test [$\chi 2$] was utilized to quantify the distinction among qualitative variables, and the Fischer exact test was utilized in situations in which the predicted cell count was less than 5. Quantitative parametric data were analyzed using independent t-test. The findings that were obtained were analyzed utilizing a significance threshold of 5%.

RESULTS

The mean age of cases with Sis was greater than that of cases without Sis respectively with a statistically significant variance among both groups [P<0.05]. The male to female ratio was 1: 1.5 without significant variance among both groups [P>0.05] as shown in Table [1].

Table [2] demonstrated that there was a significant variance among cases with and without SIs concerning HTN, DM and IHD as .value was 0.008, 0.001 and 0.022 respectively.

Table [3] demonstrated that there was a significant variance among cases with & without SIs concerning degree of stenosis at RT, LT carotid and VB as P. value was 0.003, 0.042 and 0.001 respectively.

Table [4] demonstrated that there was a significant variance among cases with and without SIs concerning their baseline Mental state as P. value was 0.046. It also demonstrated that there was a significant variance among cases with & without SIs concerning their cognitive impairment as P. value was 0.028 by MOCA.

Table [5] demonstrated that there was a significant variance among cases with and without SIs concerning Modified Rankin score as P. value was 0.016 and all cases with moderate to severe and severe disability were with Sis.

Table [1]: Comparison between patients with and without Sis regarding their age and sex

		With SIs [n = 38]	No SIs [n = 38]	Total [n = 76]	P-value
Age [years]	Mean ± SD	60.87±10.93	54.29±12.22	57.58±11.98	**0.016***
Gender, n [%]	Male	15 [39.5%]	21 [55.3%]	40 [52.6%]	0.168
	Female	23 [60.5%]	17 [44.7%]	36 [47.4%]	

Table [2]: Comparison between patients with and without SIs regarding baseline stroke risk factors

	Patients with SIs [*n* = 38]		Patients without SIs [*n* = 38]		P-value
Hypertension, n [%]	30	78.9	19	50	**0.008***
Diabetes mellitus, n [%]	22	57.9	8	21.1	**0.001***
Smoking, n [%]	16	42.1	14	36.8	0.639
Drug abuse, n [%]	2	5.3	3	7.9	0.644
Family history, n [%]	7	18.4	6	15.8	0.769
IHD, n [%]	9	23.7	2	5.3	**0.022***
AF, n [%]	10	26.3	8	21.1	0.589
BMI [mean ± SD]	30.45 ± 5.058		28.68 ± 4.988		0.128

Table [3]: Comparison between patients with and without SIs regarding their baseline degree of stenosis by duplex

		Patients with SIs [n = 38]		Patients without SIs [n = 38]		P-value
		No.	%	No.	%	
Right carotid	No stenosis	3	7.9	13	4.2	**0.003***
	< 50	25	65.8	24	63.2	
	51:70	8	21.1	1	2.6	
	> 70	2	5.3	0	0	
Left carotid	No stenosis	5	13.2	14	36.8	**0.042***
	< 50	25	65.8	21	55.3	
	51:70	6	15.8	1	2.6	
	> 70	2	5.3	2	5.3	
Vertebro-basilar	No stenosis	3	7.9	17	44.7	**0.001***
	< 50	24	63.2	19	50	
	51:70	10	26.3	2	5.3	
	> 70	1	2.6	0	0	

Table [4]: Comparison between patients with and without SIs regarding their cognitive impairment through MSE and MOCA assessment tool

		With SIs [n = 38]	No SIs [n = 38]	P-value
Mental State Examination	Mean ± SD	19.736±8.5919	23.368±6.6755	**0.046***
Montreal Cognitive Assessment Scale	Mean ± SD	18.894 ±8.50052	22.815 ±6.66112	**0.028***

Table [5]: Follow up of the Modified Rankin score after 3 months in patients with and without SIs

	With SIs [n = 38]		No SIs [n = 38]		Total [n = 76]		P value
Modified Rankin Scale	**n**	**%**	**n**	**%**	**n**	**%**	
No residual symptoms	3	7.9	9	23.7	12	15.8	**0.016***
No significant disability	7	18.4	16	42.1	23	30.3	
Slight disability	11	28.9	8	21.1	19	25	
Moderate disability	6	15.8	3	7.9	9	11.8	
Moderately severe disability	4	10.5	0	0	4	5.3	
Severe disability	3	7.9	0	0	3	3.9	
Patient has died	4	10.5	2	5.3	6	7.9	

DISCUSSION

Stroke is regarded as the primary reason for disability and the second-leading cause of mortality worldwide [5]. preventing strokes earlier and potentially more effectively could be made possible through the identification of subclinical risk factors. SBI, a potential risk factor for stroke, is an abnormality that modern MRI techniques are increasingly able to detect [6]. This research was done to detect risk factors of SBI and its effect on outcome of acute ischemic stroke.

Demographic data in our study revealed that, age was significantly higher in cases with SBI [60.8±10.9] compared with other patients

without SBI [54.2±12.2]. This was supported by two researches [7, 8], who reported that advanced age was a risk factors for silent infarcts in cases with initial ischemic stroke.

Regarding patient gender, male to female ratio was 1: 1.5 without significant difference [P value was 0.646]. This was backed by the research of **Ong *et al.*** [9] who revealed that no significant variance among cases with and without SBI regarding gender [P value 0.62]. However, **Vermeer *et al.*** [10] reported that men have significantly higher incidence of SBI compared with women. The low prevalence of males in our study thought to be fewer due to sample limitation, it could be reliable if sample size increased.

There was also a significant variance among cases with and without SBI regarding HTN, DM and ischemic heart diseases [P value was 0.008, 0.001 and 0.022 respectively].

Concerning risk factors for SBI, many researches have produced conflicting results. **Herderscheê *et al.*** [11] discovered that the three independent risk factors for SIs were age, hypertension, and smoking status.

In the study by **Kobayashi *et al.*** [12], hypertension was twofold higher in the SBI group than in those without, and the prevalence of diabetes was significantly greater in the SBI group compared to those without it. **Vermeer *et al.*** [13] found that the two most frequently acknowledged risk factors for SBI are age and hypertension, while **Oh *et al.*** [14] revealed that patients with ischemic stroke had a greater likelihood of SBI if they also had hypertension. However, there was no correlation between the two groups for other factors such as diabetes, hyperlipidemia, cardiovascular disease, hematocrit, or plasma homocysteine levels. Their results were consistent with other studies [15, 16], demonstrating a direct correlation between hypertension and the prevalence of SBI in ischemic stroke cases. Hypertension increases stroke and SBIs by enhancing atherosclerotic changes and hypoperfusion changes [17].

Assessment of SBI risk factors in this study by laboratory tests, the mean baseline random blood sugar was higher at patients with SBI group [203.97 ± 75.828] with a significant difference as P value was 0.019. Other laboratory tests [e.g. HGB, cholesterol, TG, LDL, HDL, serum uric acid] showed no significant difference among both groups. In **Akhtar *et al.*** [18] study, random blood sugar was found to be significantly higher, and diabetes increase the risk of SBI. Greater mortality, bigger lesions, and poorer functional result are all correlated with greater entry glucose levels [19].

Regarding the baseline ejection fraction in our study, there was a nonsignificant variance among cases with and without SBI and P value was more than 0.05. In the study of **Kozdag *et al.*** [20], ejection fraction and cardiac output were lesser in cases with SBI compared with those without. This difference could be cleared by sample size age [62±12] compared to [60.8±10.9] in our study as it's higher in **Kozdag *et al.*** study and all patients were previously known as cardiomyopathy.

Carotid and vertebrobasilar duplex for extra cranial arterial stenosis, right carotid, and left carotid and vertebrobasilar arteries, there was a significant variance among cases with and without SBI with P value 0.003, 0.042 and 0.001 respectively.

In the study of **Finn *et al.*** [21], two forms of atherosclerotic disease, carotid intima–media thickness [IMT] and stenosis, were both significantly correlated with SBI. In addition, **Mathiesen *et al.*** [22] reported that the prevalence of SBI was high in cases with carotid stenosis.

American stroke association [ASA] reported that atherosclerosis increase risk of SBI through two mechanisms, large artery atheromatous plaques showering emboli and small vessels hypoperfusion.

Oh *et al.* [14] revealed that although the prevalence of SBI in the large artery disease [LAD] stroke type was lesser than in the small vessel disease [SVD] stroke type, SBI was not uncommon in the LAD type. Other reports [23, 24] revealed that SBI was observed to have a greater prevalence in individuals with LAD type contrasted with the healthy Korean population.

However, **Chen *et al.*** [25] reported that neurological deficits are more severe and infarct sizes are greater in cases with multiple SBI contrasted with those with no SBI, suggesting that cases with multiple SBI may have poor collateral circulation due to the progression of large-artery or cardiovascular vasculopathy.

Stroke increases risk of cognitive dysfunction and vascular dementia. Outcome of stroke patients

in our study regarding cognitive function using MSE and MOCA after three months, there was a significant variance among cases with and without SBI as P. values were 0.046 and 0.028 respectively.

In the study of **Fang *et al.*** [26], Cognitive dysfunction and SBI have a relationship. There was no clear tendency in the data to suggest that SBI in a particular region had a greater impact on cognitive performance than those in other regions.

In a meta-analysis included 19 case-control studies with a total of 6712 individuals and three prospective cohort investigations with a total of 4433 participants, SBIs were found to be a significant factor in the loss of cognitive performance [Mini-Mental State score], based on a meta-analysis of 9 investigations. SBI was found to be a contributing factor in cognitive dysfunction [as measured by the MOCA] in a different meta-analysis of 4 trials. Decreases in some types of cognitive function were also correlated with SBI, according to ten studies. Based on these findings, it appears that SBI may not be clinically silent but rather a cause producing cognitive dysfunction [27].

There was a statistically significant distinction among cases with and without SBI on the NIHSS at baseline as well as after one week, with the mean values of the scale being greater for cases with SBI.

Multiple SBI were associated with a significantly greater NIHSS score and a greater likelihood of acute ischemic infarct of 15 mm or larger in cases with first-ever ischemic stroke without advanced leukoaraiosis by the research of **Chen *et al.*** [25]. Researchers showed that individuals with a history of multiple SBI tended to have more extensive neurological deficits and larger infarcts.

In contrast to several other investigations, we found that individuals with SBI actually had lesser strokes [28] and smaller infarct volume [28, 29].

Stoke outcome assessment also by Modified Rankin score after 3 months from onset, there was a significant variance among patients with and without SBI [P. value was 0.016] and all patients with moderate to severe and severe disability having SBI.

Unfavorable outcome of patient with SBI could be explained by **Skajaa *et al.*** [30]'s study which revealed that the recurrent stroke causes more damage than the first ever ischemic stroke and so it leads to more morbidity and mortality.

There is currently a lack of data on the long-term functional outcomes of stroke patients who experience SBI. Only a functional impact of leukoaraiosis was found in the literature. Three months and a year after the beginning of stroke, individuals with more extensive leukoaraiosis had higher MRS scores [31, 32]. This was shown using observational analyses of consecutive patients with ischemic stroke. Once the potentially confounding factor of age was taken into account, leukoaraiosis in striato-capsular infarction was found to have an inverse relationship with functional recovery [33]. The widespread neural network's capacity to adapt to a reduced functional state and compensate for the damaged structures and neural connections is a key factor in stroke recovery [34, 35].

Notable strengths exist in our investigation. They are a prospective design and a large number of patients with clinical and imaging diagnoses of stroke. The generalizability of our results is further supported by the multi-center design, which includes hospitals affiliated with Al-Azhar University [Al-Hussien and Bab ElShaeria]. Stroke and TIA survivors were not included in our research. Using individuals who had never had a stroke before helped eliminate the possibility of false Sis [such as in cases with reversible ischemic neurologic impairment].

There are some caveats to our study. First, participants were gathered from the emergency room, excluding those whose stroke was first diagnosed after several days in the intensive care unit, when they were commonly intubated and sedated. These people may get a more serious stroke. Second, because this is a hospital-based study, the incidence and severity of strokes may be overestimated because less severe patients may not have sought medical treatment or gone to the hospital. Finally, our sample size was quite limited, and we were only able to follow them for a maximum of a year. Fourth, our findings may not generalize to Asians due to the known racial differences in the occurrence of stroke subtypes. For instance, small-vessel disease is more common in Asians than in Caucasians [36]. The SBI prevalence and risk factor profiles may change between races due to the interethnic

diversity in stroke subtype prevalence. However, the current investigation gives clues regarding the prevalence and the causal risk factors of SBI in ischemic stroke.

Conclusion: Hypertension was the most significant risk factor for SBI. Patients who suffer from SBI have a greater likelihood of acquiring vascular dementia in addition to severe long-term disability and poor functional result. SBI impacts cognitive performance. In order to give precise guidelines on its long-term care, further research on the mechanism, prevention, and treatment of SBI in individuals who have had an ischemic stroke is required. In addition, further studies are required to evaluate long-term functional outcomes because the follow-up duration for most studies was short.

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