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RESEARCH

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Risk factors, clinical presentation and 1-year outcome of ischemic stroke caused by small artery disease

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Abstract

Background The prevalence of ischemic stroke (IS) caused by small-artery disease (SAD) is increasing recently. The present study aimed to report the risk factors, clinical presentations and outcome in patients presented with IS due to SAD with follow up for one year. The present study included 100 patients with IS due to SAD diagnosed on the basis of clinical and radiological findings. All patients were submitted to careful history taking, thorough clinical examination and standard laboratory work-up. Assessment of neurological functions was achieved using the National Institute of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS). Cognitive functions were evaluated using Trail making test, Stroop color word test, Arithmetic test, Vocabulary test, Wechsler adult intelligence scale IV digit span forward assessment and backward assessment. Magnetic resonance imaging (MRI) was done using a standard 1.5 Tesla unit. According to radiological findings, patients were classified into three groups: GI (n = 40) with IS due to SAD, GII (n = 30) with IS due to SAD plus internal watershed infarcts and GIII (n = 30) with IS due to SAD plus large artery infarctions (n = 30).

Results Comparison between the three groups regarding the reported risk factors identified significantly lower frequency of hyperlipidemia in GI patients as compared to GII and GIII patients (35.0% versus 60.0% and 66.7% respectively, p = 0.018). Clinically, it was shown that GI patients had significantly higher frequency of dizziness, dysphasia and tinnitus in comparison to the other two groups. It was also shown that those patients had significantly lower mean cortical thickness at the end of follow up (3.12 ± 0.9 versus 2.22 ± 0.8, p = 0.031). Finally, MRI brain volumetric study showed significantly decreased total cerebral cortical volume (TCCV) (589,456 ± 1689 versus 559,152 ± 1459) and total cerebral white matter volume (TCWMV) (521,546 ± 1785 versus 501,306 ± 1259) at the end of follow up.

Conclusions Ischemic stroke caused by small artery disease is related to poor outcome with deterioration of cognitive functions.

Keywords Ischemic stroke, Small artery disease, Stroke

Introduction

Cerebral small vessel disease (CSVD) entails a wide category of cerebrovascular lesions which basically affect the cerebral vascular network of perforating arterioles, capillaries and venules [1]. Ischemic stroke (IS) caused by small-artery disease (SAD) has increasingly become more common recently. It's claimed that SAD is responsible for 25% of IS and 45% of dementias [2].

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Identified risk factors include genetic predisposition, ageing, hypertension, vascular angiopathy, and some infections. Depending on the location of insult, clinical presentation may include cognitive decline, dementia, mood alterations, urinary incontinence and motor and gait dysfunction [3].

Radiologically, the condition may appear as subcortical infarcts, white matter hyperintensities, lacunar infarcts, perivascular spaces, microbleeds, and brain atrophy and is a frequent finding on computer tomography (CT) and magnetic resonance imaging (MRI) scans of elderly people [4].

Lacunar infarcts are small 0.2–15 mm non-cortical infarcts caused by occlusion of a single penetrating branch of a large cerebral artery These branches arise at acute angles from the large arteries of the circle of Willis, stem of the middle cerebral artery (MCA), or the basilar artery [5].

White matter lesions (WML) are ill-defined hypodensities on CT. On MRI, which is more sensitive than CT on delineating the lesions, they appear as hypointensities on T1-weighted imaging and hyperintensities on T2-weighted imaging, proton density and fluid-attenuated inversion recovery sequences (FLAIR) [6]. Unfortunately, a scarcity of studies assessed IS related to SAD in the Egyptian population. The present study aimed to report the risk factors, clinical presentations and outcome in Egyptian patients presented with IS due to SAD with follow up for one year.

Methods

The present prospective study was conducted at Tanta University Hospitals in the period from January, 2018 through January, 2019. The study was approved by the ethical committee of Tanta Faculty of Medicine (Approval code: 31105/08/16) and all patients or their legal guardians provided informed consent before enrollment in the study.

The study included 100 patients with IS due to SAD diagnosed on the basis of clinical and radiological findings. Patients were excluded if they had Parkinson disease, Alzheimer disease, demyelinating diseases or systemic or CNS vasculitis. Patients were also excluded if they were on current or recent use of acetylcholinesterase inhibitors, memantine, psychotropic drugs or antiparkinsonian drugs. Patients with prominent visual or hearing impairment or language barrier were also excluded.

All patients were submitted to careful history taking, thorough clinical examination, standard laboratory work-up and brain computed tomography imaging. Assessment of neurological functions was achieved using the National Institute of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS). Patients were classified into two categories: favorable functional outcome, defined as mRS score 0–2 and unfavorable functional outcome, with a mRS 3–5. Cognitive functions were evaluated using Trail making test, Stroop color word test, Arithmetic test, Vocabulary test, Wechsler adult intelligence scale IV digit span forward assessment and WAIS IV test digit span backward assessment. MRI was done using a standard 1.5 Tesla unit (Intera and Achiva, Philips) without prior preparation or anesthesia and after the exclusion of MRI contraindications as cardiac pacemaker.

According to radiological findings, patients were classified into three groups: GI (n = 40) with IS due to SAD, GII (n = 30) with IS due to SAD plus internal watershed infarcts and GIII (n = 30) with IS due to SAD plus large artery infarctions (n = 30). Patients in all groups were treated using the guidelines for management of IS according to the radiological and clinical findings.

Patients were followed for 12 months and were assessed at 6 and 12 months as appropriate. Data obtained from the present study were expressed as number and percent or mean and standard deviation (SD) as appropriate. Numerical variables were tested for normality using Kolmogorov–Smirnov test.

Categorical variables were compared using Fisher's exact test or chi-square test. Numerical variables were compared using t test or one-way ANOVA. All statistical calculations were operated using SPSS 25 (IBM, USA) with p value < 0.05 considered statistically significant.

Results

The present study included 100 patients with IS due to SAD. According to radiological findings, patients were classified into three groups: GI (n = 40) with IS due to SAD, GII (n = 30) with IS due to SAD plus internal watershed infarcts and GIII (n = 30) with IS due to SAD plus large artery infarctions (n = 30). Comparison between the three groups regarding the reported risk factors identified significantly lower frequency of hyperlipidemia in GI patients as compared to GII and GIII patients (35.0% versus 60.0% and 66.7% respectively, p = 0.018). Clinically, it was shown that GI patients had significantly higher frequency of dizziness, dysphasia and tinnitus in comparison to the other two groups. In contrast, patients in GII and GIII had significantly higher frequency of right and left hemiparesis when compared to GI. Also, it was found that GI patients had significantly higher rate of recombinant tissue plasminogen activator (rTPA) use, higher rate of unfavorable outcome and higher mortality rate as compared to the other two groups (Table 1).

Table 1 Clinical data in the studied groups

	GI N = 40	GII N = 30	GIII N = 30	p value
Age (years) mean ± SD	65.0 ± 9.0	69.0 ± 9.5	68.0 ± 9.0	0.32
Male/female n	22/18	20/10	18/12	0.62
Rural/urban n	18/22	15/15	16/14	0.49
Risk factors n (%)				
Diabetes mellitus	26 (65.0)	18 (60.0)	22 (73.3)	0.54
Hypertension	18 (45.0)	14 (46.7)	14 (46.7)	0.99
Hyperlipidemia	14 (35.0)	18 (60.0)	20 (66.7)	0.018
Obesity	12 (30.0)	8 (26.7)	4 (13.3)	0.32
Cardiac disease	20 (50.0)	14 (46.7)	12 (40.0)	0.71
Smoking	18 (45.0)	10 (33.3)	10 (33.3)	0.50
Drug abuse	8 (20.0)	4 (13.3)	10 (33.3)	0.26
Stroke	20 (50.0)	20 (66.7)	16 (53.3)	0.36
Homocystinemia	18 (45.0)	16 (53.3)	20 (66.7)	0.20
Clinical findings n (%)				
Dizziness	4 (10.0)	–	–	0.044
Dysphasia	8 (20.0)	4 (13.3)	–	0.038
Headache	6 (15.0)	2 (6.7)	–	0.069
Left ataxic hemiparesis	4 (10.0)	10 (33.3)	–	0.001
Left hemihypothesis	6 (15.0)	2 (6.7)	–	0.069
Right hemiparesis	–	6 (20.0)	14 (46.7)	< 0.001
Left hemiparesiss	–	4 (13.3)	12 (40.0)	< 0.001
Tinnitus	6 (15.0)	–	–	0.008
Unsteadiness	6 (15.0)	2 (6.7)	4 (13.3)	0.55
Treatment n (%)				
Regular treatment	34 (85.0)	30 (100.0)	30 (100.0)	0.008
rTPA	6 (15.0)	–	–	
Hospital stay (days) mean ± SD	9.2 ± 2.8	8.1 ± 1.9	7.7 ± 3.1	0.053
Outcome n (%)				
Favorable	10 (25.0)	11 (36.7)	13 (43.3)	0.84
Unfavorable	16 (40.0)	15 (50.0)	15 (50.0)	
Mortality n (%)	14 (35.0)	4 (13.3)	2 (6.7)	0.007

During follow up, 20 patients died in all groups. Survivors were followed for 12 months for assessment of clinical improvement. No significant differences were noted during follow up regarding NIHSS and mRS score. However, there was significant decline in freezing scale at 6 and 12 months in comparison to baseline (56.2 ± 2.6 versus 48.2 ± 5.1 and 43.2 ± 6.2, p = 0.041). Trail making test and Stroop color word test score significantly increased at the end of follow up while arithmetic test and vocabulary test scores significantly declined (Table 2).

Radiologically, patients experienced significantly increased number of occult lacunar brain infarcts at the end of follow up (0.56 ± 0.21 versus 1.77 ± 0.51, p = 0.001). In cortico-spinal diffusion tensor tractography, there were significant decline of fractional anisotropy (FA) (0.62 ± 0.13 versus 0.51 ± 0.21, p = 0.022) and cortico-spinal tract (CST) (388.0 ± 29.0 versus 321.0 ± 56.0, p = 0.009) at the end of follow up. Likewise, there were significant decline of FA on thalamao-cortical connectivity diffusion tensor tractography (0.75 ± 0.12 versus 0.41 ± 0.15, p = 0.001) and arcuate fasciculus diffusion tensor tractography (0.47 ± 0.02 versus 0.36 ± 0.06, p = 0.001). It was also shown that patients had significantly lower mean cortical thickness at the end of follow up (3.12 ± 0.9 versus 2.22 ± 0.8, p = 0.031). Finally, MRI brain volumetric study showed significantly decreased total cerebral cortical volume (TCCV) (589,456 ± 1689 versus 559,152 ± 1459) and total cerebral white matter volume (TCWMV) (521,546 ± 1785 versus 501,306 ± 1259) at the end of follow up (Table 3).

Discussion

In the present study we recognized multiple risk factors for IS due to SAD. These included diabetes mellitus, hypertension, hyperlipidemia, obesity, cardiac disease, smoking homocystinemia, drug abuse and previous stroke. These findings are in agreement with the studies of Cohen et al. [7], Zeng et al. [8] and Ueno et al., [9]. Interestingly, the study of Shi et al., [10] identified hypertension, diabetes mellitus, high total cholesterol, hypertriglyceridemia and smoking as risk factors for small vessel disease and large artery atherosclerosis. In our work, 60% of affected patients are men in contrast to Palm et al. [11] study where women with IS due to SAD outnumbered men.

During 1-year follow up in this study, 20% of patients died. The overall mortality rate for all IS patients in the study of Bryndziar et al. [12], 29.4% with no significant differences between patients with small and large artery occlusions. In comparison, the study of Zhao et al. [13] on 1464 SAD patients, the 1-year mortality rate was only 3.1%. In another study, the average 1-year mortality rate was 6.5% [14]. This variation among different studies is probably related to underlying comorbidities or associated cerebral injuries.

In the present study, patients with co-existing small and large artery disease had significantly higher rate of hemiparesis in comparison with the other two groups. These findings are supported by previous reports. In the study of Fu et al. [15] co-existing small vessel disease was associated with poor outcome in stroke patients with multiple intracranial large arteries atherosclerosis. Also, the study of Ntaios et al. [16] found that in diabetic stroke patients, those with large-artery atherosclerotic strokes had more severe presentation and poor outcome when

Table 2 Neurological findings in survivor group

	Baseline	6 months	12 months	p value
NIHSS n (%)				
Mild	30	30	36	0.1
Moderate	30	32	16	
Severe	20	18	18	
mRS score n (%)				
0	–	–	–	0.86
1	12	12	14	
2	20	22	20	
3	30	28	28	
4	18	18	18	
5	–	–	–	
Freezing scale mean ± SD	56.2 ± 2.6	48.2 ± 5.1	43.2 ± 6.2	0.041
Neuropsychiatric scales mean ± SD				
Trail making test	252.0 ± 19.0	274.0 ± 22.0	295.0 ± 26.0	0.039
Stroop color word test	112.0 ± 20.0	135.0 ± 25.0	175.0 ± 19.0	0.011
Arithmetic test	17.9 ± 0.4	15.2 ± 0.4	12.2 ± 0.5	0.029
Vocabulary test	40.9 ± 2.1	33.9 ± 1.9	28.2 ± 2.1	0.019
WAIS IV test digit span forward assessment	4.5 ± 0.4	4.5 ± 0.6	4.6 ± 0.4	0.57
WAIS IV test digit span backward assessment	4.2 ± 0.4	4.2 ± 0.6	4.3 ± 0.4	0.6

WAIS IV Wechsler adult intelligence scale IV

Table 3 Radiological findings in survivor group

	Baseline	6 months	12 months	p value
Periventricular hyperintensity n (%)				
Absent	–	–	–	0.89
Cell lining	20	21	21	
Smooth(halo)	10	10	10	
Irregular	10	9	9	
Occult lacunar brain infarcts mean ± SD	0.56 ± 0.21	–	1.77 ± 0.51	0.001
Cortico-spinal diffusion tensor tractography mean ± SD				
FA	0.62 ± 0.13	–	0.51 ± 0.21	0.022
CST (density)	388.0 ± 29.0	–	321.0 ± 56.0	0.009
Thalamao-cortical connectivity diffusion tensor tractography mean ± SD				
FA	0.75 ± 0.12	–	0.41 ± 0.15	0.001
TCC	666.9 ± 74	–	649.2 ± 49	0.547
Arcuate fasciculus diffusion tensor tractography mean ± SD				
FA	0.47 ± 0.02	–	0.36 ± 0.06	**0.001**
TCC	230.33 ± 74	–	237.14 ± 49	0.273
Mean cortical thickness	3.12 ± 0.9	–	2.22 ± 0.8	**0.031**
MRI brain volumetric study				
TCCV (mm^3)	589,456 ± 1689	–	559,152 ± 1459	**0.001**
TCWMV (mm^3)	521,546 ± 1785	–	501,306 ± 1259	**0.012**

TCC Thalamao-cortical connectivity, *FA* Fractional anisotropy, *CST* Cotico-spinal tract, *FA* Fractional anisotropy, *TCCV* total cerebral cortical volume, *TCWMV* total cerebral white matter volume

compared with patients with small-vessel occlusion strokes. Moreover, it was noted that the presence of co-existing small-vessel disease is associated with recurrent stroke in patients with large artery atherosclerosis [17].

In our study, follow up of patients identified multiple significant changes in the neurological and psychometric findings in the survivor group reflecting a trend towards more cognitive decline at 1-year in line with the conclusions of Jiménez-Balado et al. [18]. In contrast, Yang et al. [19] recognized strong improvement especially in executive function after 1 and 6 months of stroke.

In addition, we could detect multiple radiological changes in the studied patients during follow up. These data are in line with the results of Haque et al. [20] who noted significant decrease in subcortical volumes of the thalamus, hippocampus, and amygdala and cortical thickness of the entorhinal and perirhinal cortices and cingulate gyrus at 12 months. Likewise, the study of Chen et al. [21] found significant decreases of cortical thickness in cerebral hemispheres of the ischemic stroke patients.

Conclusions

Ischemic stroke caused by small artery disease is related to poor outcome with deterioration of cognitive functions. The condition may be affected by other concomitant cerebral insults.

Recommendation

Ischemic stroke patients with suspected SAD should be submitted to MRI examination for better identification of the cerebral lesions. Detailed evaluation for comorbidities contributing to small vessel damage, optimal control of vascular risk factors, quantitative MRI monitoring for subclinical progression, and early initiation of cognitive rehabilitation are suggested to improve outcome. Further studies are needed to improve the current guidelines for diagnosis and management of ischemic stroke associated with SAD.

Abbreviations

CNS	Central nervous system
CST	Cotico-spinal tract
CSVD	Cerebral small vessel disease
CT	Computer tomography
FA	Fractional anisotropy
FLAIR	Fluid-attenuated inversion recovery sequences
IS	Ischemic stroke
MCA	Middle cerebral artery
MRI	Magnetic resonance imaging
mRS	Modified Rankin scale
NIHSS	National institute of health stroke scale
SAD	Small-artery disease
TCC	Thalamao-cortical connectivity
TCCV	Total cerebral cortical volume
TCWMV	Total cerebral white matter volume
WAIS	Wechsler adult intelligence scale
WML	White matter lesions

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Author contributions

TE, HF, AE, ME, and MA, Conceived and designed the experiments: TE, HF, AE, and ME, enrolled the patients: HF, AE, ME, and MA Performed the experiments: TE, HF, AE, ME, and MA, data management and analysis: TE, HF, AE, ME, Contributed reagents/materials/analysis tools: AE, ME, and MA, prepared the manuscript: TE and ME, read and approve the manuscripts: TE, HF, AE, ME, and MA. All authors read and approved the final manuscript.

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Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The present prospective study was conducted at Tanta University Hospitals in the period from January, 2018 through January, 2019. The study was approved by the ethical committee of Tanta Faculty of Medicine (Approval code: 31105/08/16) and all patients or their legal guardians provided informed consent before enrollment in the study.

Informed consent

Written informed consent was obtained from all patients or their legal guardians before enrollment in the study.

Consent for publication

Not applicable.

Competing interests

There are no conflicts of interest.

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