Acta Neurophysiologica

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Research Article *Volume 4 Issue 2*

Cerebral Small Vessel Disease Markers in the Patients with Ischemic Stroke at a Tertiary Care Hospital

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Received Date: February 10, 2023; **Published Date:** March 28, 2023

Abstract

Objective: In patients with ischemic stroke, we studied the markers and risk factors of cerebral small vessel disease at a tertiary care hospital.

Methods: An observational study was conducted in patients with ischemic stroke. MRI based markers of small vessel disease of brain White matter hyper intensity, Microbleed, Lacunae and Perivascular spaces were determined by visual analysis by STRIVE criteria and grouped to obtain SVD score which was compared to risk factors in the patients.

Results: In 142 patients studied during October 2019 to march 2020 with ischemic stroke, large vessel occlusion was found in 26.4%, cardio embolic in 27.4% and other etiology in 46.2% of patients. Average age of the group was 63 years with male predominance (63.3%), hypertension was most common risk factor (71.1%), followed by diabetes mellitus (38.7%), old cerebrovascular and cardiovascular disease was found in 32.4% and 28.8% of patients respectively. Uncontrolled Hba1c was found in 37.3%, low HDL was seen in 56.3% and raised LDL levels were seen in 47.8%.SVD score '0' was seen in 35.9% and remaining 64.1% at least one markers of severe SVD score. There was no association of stroke subtypes with severity of cSVD score (p-value >0.05).

Conclusion: cerebral Small vessel disease is significant risk factor in not only lacunar stroke, but also in large vessel occlusion and cardio embolic stroke. It may confound the risk with other traditional risk factors. Its estimation may help in proper stratification, prognostication and treatment of cSVD.

Keywords: Hyper Intensity; Microbleed; Lacunae; Perivascular Spaces; Cerebrovascular; Cardiovascular Disease

Abbreviations: cSVD: Cerebral Small Vessel Disease; WHM: White Matter Hyperintensity; PVS: Perivascular Space; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein.

Introduction

Small vessel disease is a term used with various meanings and in different contexts (i.e., pathological, clinical, and neuroimaging aspects). Cerebral small vessel disease (cSVD) indicates cumulative different pathological processes that affect the small vessels of the brain, including small arteries, arterioles, capillaries, and small veins. These diseases are thought to be the most frequent pathological neurological processes and have a crucial role in at least these fields: stroke, dementia, Parkinsonism and ageing [1] cSVD has a crucial role in lacunar cerebral infarction accounting for up to 25% of all ischemic strokes and deep or cortical

hemorrhages. Lacunar infarction is secondary to micro vascular thromboembolism episodes.

Cognitive decline and dementia, gait problems are also frequently associated with cSVD [2]. There seems to be a complex inter- relationship between Alzheimer's disease and cerebrovascular disease. White matter hyperintensities, microbleeds and lacunar infracts in strategically located location is known to be associated with Dementia and cognitive dysfunction especially in executive function domain. Parkinson's disease is associated with cerebral Small vessel disease due to interruption in with basal ganglia-thalamocortical circuits involving both the frontal and parietal lobes. Large intraparenchymal hemorrhages, gait imbalance, Depression are also associated with cerebral Small vessel disease.

In ischemic lesions caused by small vessel disease, the vessel lumen restriction is thought to lead to a state of chronic hypo perfusion of the white matter, eventually resulting in degeneration of myelinated fibers as a consequence of repeated selective oligodendrocyte death. White matter damage is thought to be a form of incomplete infarct or selective necrosis similar to what has been described for neurons [3].

Study Design

This is a hospital based observational study in which participants who presented to hospital with ischemic stroke and underwent MRI Brain as a part of their evaluation were studied for markers of cerebral small vessel disease. Inclusion criteria was patients with age >18 years, ischemic stroke with clinical signs of focal or global disturbance of cerebral function lasting ≥24 hours. MRI Brain showing ischemic stroke and one of the marker of cerebral small vessel disease (White matter hyper intensity - Peri Ventricular - Fazeka 3, Deep-Fazeka-2 or 3, microbleed, Lacunae, enlarged perivascular spaces >10).Patients with age less than 18 and if no MRI brain was available for evaluation.

The participants presenting to hospital will undergo through evaluation by clinical history and physical examination, MRI Brain and appropriate laboratory investigations. Stroke was classified into large artery atherosclerosis (> 50% stenosis of a major brain artery or branch cortical artery), cardioembolic (history of myocardial infarction, EF<35%, atrial fibrillation, atrial septal defect etc.), small vessel disease (lacunar infarct, with either markers of small vessel disease). Lacunar infarct was defined as an acute stroke syndrome with a lesion compatible with the occlusion of a single perforating artery, consisting of a subcortical (basal ganglia, internal capsule, brainstem), small, sharply demarcated lesion with a diameter <15 mm.

MRI Brain Protocol

MRI brain was performed on 3T MRI brain (Siemens) and following sequences were obtained: T1 weighted sequence, T2 weighted sequence, fluid-attenuated inversion recovery sequence, Diffusion weighted imaging, and susceptibility weighted imaging. Patients with Stroke underwent Intracranial and extra cranial angiography.

The markers of small vessel disease of Brain on MRI are [4]:

- **White Matter Hyper Intensity:** Deep and periventricular WMH were both graded according to the Fazekas scale from 0 to 3.
- **Micro Bleeds:** small (5 mm), homogeneous, round foci of low signal intensity on gradient echo images in cerebellum, brainstem, basal ganglia, white matter, or cortico-subcortical junction.
- **Lacunes:** rounded or ovoid lesions, 3-20 mm in diameter; in the basal ganglia, internal capsule, centrum semiovale, or brainstem; of CSF signal intensity on T2 and FLAIR, generally with a hyperintense rim on FLAIR and no increased signal on DWI.
- **Enlarged Perivascular Spaces:** 3 mm punctate (if perpendicular) and linear (if longitudinal to the plane of scan) hyperintensities on T2 images in the basal ganglia or centrum semiovale.

MRI burden of Small vessel disease of brain: the total MRI burden of SVD on an ordinal scale from 0 to 4, by counting the presence of each of the 4 MRI features of SVD.

❖ **Small Vessel Disease Score** [5]:

White Matter Hyperintensity	Peri Ventricular –Fazeka 3 or Deep-Fazeka -2 or 3	1 point
Microbleed	1 or more bleed	1 point
Lacuane	1 or more lacunae	1 point
Enlarged Perivascular Spaces	>10 in number	1 point
Total		4 points

The data collected in Microsoft excel sheet and analyzed by software SPSS version 23, Frequencies, Chi-square test and logistic regression were done.

Results

A total of 142 patients with ischemic stroke were evaluated for markers of cerebral small vessel disease. 93 patients were found to have at least one marker of cSVD. The characteristics of patients are summarized in below given Table 1.

TOTAL patients(n)	142	
AGE	Mean age-63 YR	Range :20-87 YEARS
GENDER(F:M)	52:90	M:63.3%
HYPERTENSION	101	71.10%
DIABETES	55	38.70%
THYROID DISORDER	15	10.50%
Old CAD	41	28.87%
Old CVA	46	32.40%
DYSLIPIDIEMIA	36	25.35%
SMOKING	45	31.69%
HbA1C >/=6.6	53	37.30%
VITAMIN-B12<200	14	9.80%
CHOLESTEROL >200 mg/dl	22	22(15.4%)
TRIGLYCERIDES>150 mg/dl	36	36(25.3%)
HDL<40 mg/dl	80	80(56.3%)
LDL>100 mg/dl	68	68(47.8%)
SVD-0	51	35.91%
SVD-1	28	19.71%
SVD-2	35	24.64%
SVD-3	18	12.67%
SVD-4	12	8.40%

Table 1: Characteristics of the patients in the study.

Among the patients with at least one marker of cSVD, the mean age of patients was around 68.8 years, with age ranging from 37-87 years. The age more than 55 years was found 84.9% of patients. There was male predominance with 62.4% of total patients. The risk factors studied were hypertension found in 77.4%, diabetes mellitus in 45.2%, past history of CAD – in 33.3% and old CVA in 39.8%, and smoking in 40.9% (Table 2).

	Odds Ratio(95% CI)
Age	1.205(0.664-2.148)
Hypertension	1.147(0.696-1.892)
Diabetes	1.229(0.813-1.858)
CAD	1.016(0.659-1.568)
CVA	1.168(0.77-1.773)
Smoking	0.805(0.546-1.232)

Table 2: Risk factors associated with cSVD and their odds ratio.

Age more than 55 years of age; presence of hypertension, diabetes, old CVA had increased odds of developing severe cSVD markers. Old CAD had modest increase in odds ration where as smoking as not associated with increased odds of developing cSVD. Serum Hba1c levels was raised in 37.3%. Low HDL was seen in 56.3% and raised LDL levels were seen in 47.8%, high serum cholesterol was found in 15.4% and high triglycerides was associated with 25.3% of patients.

Large vessel occlusion was found in 26.4%, cardioembolic in 27.4% and other etiology in 46.2% of patients. MRI brain showed at least one marker of cerebral small vessel disease in 64.09%.Lacunar strokes were found in 31.1%. White matter hyper intensity was seen in 40.1%, microbleed in 36.6%, lacunae in 28.8% and perivascular spaces in 40.8%. These cSVD markers when estimated as SVD score are described as in table below.

The different subtypes of stroke when evaluated for different scores of cSVD are shown in the table. There was no significant association between cSVD score and different subtypes of stroke (p value>0.05). Similarly there was no significant association between cSVD scores and lacunar stroke (p value >0.05) (Table 3).

	Total-142	SVD-1	SVD-2	SVD-3	SVD-4
Large vessel disease	37	7 (30.4%)	8 (34.7%)	5(21.7%)	3(13.2%)
Cardioembolic	39	4 (16.6%)	14 (58.3%)	5(20.8%)	1(4.3%)
Small vessel disease	66	17 (37%)	13 (28.2%)	8(17.4%)	8(17.4%)

Table 3: Subtypes of stroke and distribution of SVD score.

Discussion

The term small vessel disease encompasses all the pathological processes that affect the small vessels of the brain, including small arteries and arterioles but also capillaries and small veins. The mechanisms that link small vessel disease with parenchyma damage are heterogeneous and not completely known. Pathological changes in the small vessels can lead to both ischemic and hemorrhagic consequences. In ischemic lesions caused by small vessel disease, the vessel lumen restriction is thought to lead to a state of chronic hypoperfusion of the white matter, eventually resulting in degeneration of myelinated fibers as a consequence of repeated selective oligodendrocyte death. White matter damage is thought to be a form of incomplete infarct or selective necrosis similar to what has been described for neurons [3].

Acute occlusion of a small vessel is hypothesized to occur, leading to focal and acute ischaemia and complete tissue necrosis (pannecrosis), this is the putative mechanism of lacunar infarcts. Other mechanisms such as blood–brain barrier damage local subclinical inflammation, and oligodendrocyte apoptosis could be involved in the so-called ischaemic forms of small vessel disease and contribute to the final pathological picture [6]. Pathogenesis includes alteration in blood-brain barrier and pathogenesis of cerebral small vessel disease. Traditional risk factors such as hypertension or diabetes mellitus play their important role in development of cSVD, but the exact pathogenesis of cSVD is still unclear. Increased permeability of the BBB and endothelial dysfunction has been found to be associated with cSVD. BBB disruption is important pathological features of cSVD. Thus, circulating biologic markers of endothelial dysfunction might play a crucial role in identification of cSVD2.

The other factors include Interaction among cellular components of BBB in cerebral small vessel disease. Abnormal endothelial functioning alone is not responsible in development of cSVD pathology. For the maintenance of BBB, other cellular components such as pericytes, astrocytes, and OPCs, are also thought to be essential although their exact contribution is yet to known. In fact, the impact of disrupted cross talk among BBB cell components in this regard is of great significant in understanding molecular mechanism and early phase identification of disease [2]. Increased large artery stiffness transmits the excessive flow pulsatility into the cerebral microcirculation as well as causing diastolic hypoperfusion which both damage microvascular wall thus leading to arteriolosclerosis and white matter damage [7,8]. Therefore, it would not be incorrect to say that both small and large artery disease make a continuum and interact dynamically. Models that have demonstrated disruption of the endothelial tight junction and increase of white matter disease in animal models with bilateral common carotid artery (CCA) stenosis [9].

The etiopathological classification of small vessel disease included into 6 subtypes – atherosclerosis, cerebral amyloid angiopathy, inherent/ genetic small vessel disease, inflammatory and immunologically mediated small vessel disease, venous collagenosis and other diseases likes post radiation angiopathy. The study by Hopkins et al. [10], 2006 showed that, age > 55 years is associated with more than 10 fold increase in prevalence of White matter hyperintensities. Indonesian stroke registry also showed > 55 years of age as a significant risk factor for small vessel disease of brain in stroke patients [11]. The prevalence and severity of small vessel disease of brain increases with increasing age. Younger patients have fewer markers and as age increases, the severity of SVD increases. Older patients have more common vascular risk factors like atherosclerosis, hypertension, Diabetes and dyslipidemia.

The gender difference in risk factors like hypertension, diabetes mellitus and dyslipidemia may have influence on incidence of small vessel disease of brain. Staals, et al. [6] and Lau, et al. [12], had higher proportion of male in their study which as associated with severity of cSVD. Hypertension was associated with SVD score severity. Harris, et al. [13] (77%), Staals, et al. [5] (65%), Wei, et al. [14] (69%) Prolonged elevation of Blood pressure causes chronic changes in microcirculation by remodeling of arteriole and reduction in compliance of arterioles and capillaries leading to lipohyalinosis and atherosclerosis.

Diabetes mellitus, insulin resistance and hyperglycemia lead to oxidative stress, inflammation and advanced glycation end products which can induce microvascular abnormality. Our study showed positive association with SVD score like Huo, et al. [15], and Lau, et al. [12], while Staals, et al. [5], and Hilal et al. [11] showed no positive correlation with diabetes. Our study showed positive correlation between Old CVA/CAD

with SVD score severity similar to studies like Lau, et al. [12], Huo, et al. [15], Studies from Staals, et al. [5], did not find positive correlation between Old CVA/CAD and SVD score severity.

In our study there was no significant relation between SVD score and Lacunar stroke syndrome. Staals, et al. [5], showed that patient with Lacunar stroke had higher SVD score when compared to patients with cortical infract. Epidemiological study to differentiate cortical and subcortical stoke done by Dullie, et al. showed incidence of cortical stroke of around 66.7%. There was no correlation between SVD score severity and Cortical or Deep infarct in our study.

Studies have shown that markers of small vessel of disease are associated with recovery after stroke and recurrent stroke and morbidity and associated with cognitive decline in stroke patients [16,17]. Treatments of SVD include non-pharmacological intervention like physical activity and medditerean diet. The Look AHEAD study tested a 10-year physical activity and dietary modification intervention in older adults who are overweight and obese with type 2 diabetes mellitus. Although there was no effect of the intervention on cognition in the MRI substudy, the intervention group had significantly lower WMH volume than the control group [18].

Pharmacological intervention includes control of hypertension. Treatment with an angiotensin-converting enzyme (ACE) inhibitor over 36 months reduced the WMH number and total WMH volume in the Perindopril Protection Against Recurrent Stroke Study trial (PROGRESS) [19]. The results of the Systolic Blood Pressure Intervention Trial (SPRINT-MIND) of intensive versus standard blood pressure control on WMH were presented at Alzheimer's Association International Conference 2018. This trial demonstrated reduced mild cognitive impairment in the intensive treatment arm (though this was not a primary endpoint of the trial) [20]. The limitation of this study include retrospective cross section observational study, small size of the study, visual estimation of markers of small vessel of disease which may have inter observational variations, estimation of presence of markers as a global marker of brain instead of estimating it according to lobe or specific areas of brain like basal ganglia, brainstem or cerebellum.

Conclusion

Cerebral Small vessel disease of brain is significant risk factor in subtypes ischemic stroke including Large vessel occlusion, Cardioembolic and lacunar stroke. Age , hypertension, diabetes mellitus , old CVA/CAD are significantly associated with severe cSVD . Further studies with larger sample size estimating the progression of SVD and estimating outcomes based on stratification of lesion based on load and location will help in better understanding the effect of SVD on stroke.

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