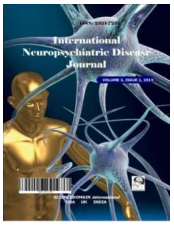

International Neuropsychiatric Disease Journal
6(4): 1-9, 2016; Article no.INDJ.22819
ISSN: 2321-7235, NLM ID: 101632319

SCIENCEDOMAIN *international*
www.sciencedomain.org

Black Holes in Brain- Is There Any Relationship between Carotid Artery Plaque Type and Cerebral Micro Bleed? - Cohort from Pakistan

Fatima Mubarak[1*], Shayan Sirat Maheen Anwar[1] and Kainat Baig[1]

[1]Department of Radiology, Aga Khan University Hospital, Karachi, Pakistan.

Authors' contributions

This work was carried out in collaboration between all authors. Author FM designed the study and wrote the protocol. Authors KB and SSMA preformed the statistical analysis, managed the literature search and wrote the first draft of the manuscript with assistance from author FM. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/INDJ/2016/22819
Editor(s):
(1) Elena Cecilia Rosca, Department of Neurology, University of Medicine and Pharmacy, Romania.
(2) Vincenzo La Bella, Department of Clinical Neurosciences, ALS Clinical Research Center, University of Palermo, Italy.
(3) Zhefeng Guo, Department of Neurology, University of California, Los Angeles, USA.
Reviewers:
(1) Paul Schoenhagen, Cleveland Clinic, Cleveland, OHIO, USA.
(2) Abrao Rapoport, Sao Paulo Unversity, Brazil.
Complete Peer review History: http://sciencedomain.org/review-history/13551

Original Research Article

Received 29th October 2015
Accepted 5th January 2016
Published 4th March 2016

ABSTRACT

Purpose of Study: The purpose of this study is to correlate the presence of chronic micro bleed, patient symptoms, number of chronic micro bleeds and carotid plaque characteristics.
Materials and Methods: Seventy consecutive patients (50 men, 20 women; mean age 64.5; range 45-82 years) were selected for the study. We took every patient's ipsilateral internal carotid artery and cerebral hemisphere individually. Each patient underwent MRI brain with stroke protocol and ultrasound carotid Doppler for suspected carotid pathology. Chronic micro bleeds were classified by an ordinal scale and carotid plaques were characterized based on their composition, that is, fatty, mixed, or calcified. Patients were classified as symptomatic and asymptomatic. Receiver operating characteristic (ROC) curve were created. Correlation was done to see association between the number of chronic micro bleeds, their symptoms and relationship of plaque type with chronic micro bleeds.
Results: The prevalence of chronic micro bleed was 42.8% (60/140) over all, with prevalence of

**Corresponding author: E-mail: mubarakfatima@hotmail.com;*

61.53% in symptomatic sides. A statistically significant difference between chronic micro bleeds presence was observed, with a P value of <0.0001 and an Odds ratio of 4.4 with 95% confidence interval of range 2.15 to 8.99.
Statistically significant direct correlation with the fatty / soft plaques (correlation coefficient = 0.177; P value = 0.018). No statistically significant association was detected between CMBs and mixed plaque type (correlation coefficient 0.090; P value .145). We also performed the ROC curve analysis for symptomatic (stroke and TIA) and asymptomatic sides and the results were: 0.7849 and 0.6181 respectively, confirming that there is an association between CMBs and symptomatic (stroke/TIA) patients, but no association between CMBs and asymptomatic patients.
Conclusion: This study shows there is increasing trend of chronic micro bleeds with fatty plaques. Moreover, chronic micro bleeds are prevalent in patients who have stroke or transient ischemic attacks.

Keywords: Carotid artery Doppler; plaque type; cerebral micro bleed; GRE T2-weighted MRI.*

1. INTRODUCTION

Cerebral micro bleeds (CMBs) are increasingly been reported in patients with ischemic stroke with the use of GRE T2*-weighted sequence in MR brain imaging [1].

Micro bleeds are rounded, small hypointensities within brain parenchyma which indicate small vessel disease in patients suffering from hypertension, diabetes or cerebral Amyloid angiopathy [1].

Besides affecting cognition function of brain, [2] CMBs have been proposed to increase risk of bleeding complications from thrombolytic treatment or the use of antiplatelet drugs in ischemic stroke, [3].

Little has been explored so far to establish the cause of CMBs, whether they are a consequence of systemic disease or an expression of localized carotid artery plaque disease [4].

The hypothesis we seek in this study is whether there is an association between the presence of CMBs and the presence/characteristics of carotid plaque. Within the last few years, it was evidenced that the composition of the carotid plaque plays a fundamental role in stroke risk assessment [5-9].

Considering it as an excellent, cost-effective and safe imaging modality, we utilized Colour-Doppler Sonography (CDS) to assess plaque characteristics. The accuracy of colour-Doppler sonography is comparable to that of multidetector row CT angiography (MDCTA) in evaluating the degree of geometric stenosis caused by the plaque; in addition, it provides functional information on the plaque's hemodynamics effects [10,11].

We will test our hypothesis both by analyzing carotid plaque composition and CMBs presence. Cartoid plaque composition will be analyzed using CDS, whereas presence of CMBs will be seen using MR imaging. To our knowledge no such study has been conducted so far on national level.

2. MATERIALS AND METHODS

We created a database from retrospective case material, belonging to our institution, and then searched this database prospectively as a hypothesis-driven scientific study. Inclusion criteria were 40 plus years of age and previous MRI imaging of the brain as well as ultrasound carotid arteries performed at the same setting, whereas exclusion criteria were other possible causes of white matter diseases such as multiple sclerosis, vasculitis, acute disseminated encephalomyelitis or connective tissue diseases.

From January 2009 till December, 2014; 70 consecutive patients (50 men, 20 women; mean age 64.5; range 45-82 years) met the above mentioned criteria in our university hospital and were selected for the study. For the analysis of the data, we considered the carotid and cerebral hemisphere of each side as an independent unit. Therefore, the total number of studied carotid arteries and brain hemispheres was 140. Each patient underwent MRI brain with stroke protocol and ultrasound carotid Doppler for suspected carotid pathology.

Demographic details including age, gender, and risk factors were recorded. This retrospective review evaluated existing clinical data and records. No additional procedures were

performed. The review was conducted in accordance with guidelines of the research committee of our institution.

Cerebrovascular systems were classified as symptomatic or asymptomatic. Symptomatic patients were those who had TIA or stroke. TIA is a condition when deficits lasts <24 hours and stroke when symptoms lasts>24 hours.

Asymptomatic patients were those who had a remote stroke >6 months but had MRI brain with stroke protocol and Ultrasound carotid Doppler.

Coronary artery disease, high BP, dyslipidemia, diabetes and cigarette smoking were considered as risk factors according to WHO guidelines.

2.1 Ultrasound Carotid Doppler Technique

All patients underwent Ultrasound carotid Doppler on Xario Toshiba Machine. It included evaluation of the entire course of the accessible portions of bilateral common carotid and internal carotid arteries. Equipment gain and display settings were optimized while imaging was done with respect to depth, dynamic range and focal zones. Color flow Doppler was added to supplement B mode images with proper scale to demonstrate areas of high flow and color aliasing. Power Doppler was used to validate flow states or occlusion. Cursor sample size was small and positioned parallel to the vessel and or direction of blood flow. A spectral Doppler angle of 60 degrees or < was used to measure velocities. Spectral Doppler wave forms and velocity measurements were recorded at and distal to the stenosis or obstruction.

2.2 Brain MRI Technique

We have standardized the stroke protocol. Examinations were performed on 1.5T Siemens and 3T Toshiba Vantage with head coil.

In all participants, convential 2DT2*-weighted GRE MR imaging was performed (TR shortest; TE 23 ms; flip angle 15 degree; in plane resolution 0.9-0.9; FOV 230 mm, matrix 512-512; section thickness 5 mm; 0.5 mm intersection gap).

DWI acquired with values of 0, 500 and 1000 Bo and ADC with only 1000 Bo on 3T.

In addition sagittal T2W, axial T1W and T2W and FLAIR sequences were acquired with same section thickness.

2.3 Cerebral Micro Bleeds (CMB) Classification

All images were reviewed for the presence of CMBs. The presence and number of all cerebral micro bleeds were recorded. In our study, CMB were considered as focal, rounded or circular areas of very low signal intensity that were smaller then 10 mm in size as suggested by Jeerkathil et al. According to the consensus guidelines on standards for neuroimaging cognitive impairment, 2 mm was taken as the lower limit for size of micro bleed.

Micro bleeds were classified as absent (grade 1), mild (grade 2; total no of micro bleeds 1-2), moderate (grade 3; 3-10) and severe (grade 4; >10) according to LEE and colleagues.

2.4 Carotid Artery Plaque Classification

Ultrasound images were analyzed blinded to MRI and patients history. We categorized different types of plaques dividing them into soft plaque (hypo echoic), mixed plaque (heterogeneous) and calcified (with posterior shadowing).

2.5 Statistical Analysis

ROC curve analysis was performed to identify thresholds in number of CMBs associated with presence of symptoms.

SPSS version 19 was used for statistical analyses.

3. RESULTS

3.1 Correlation Analysis Demonstrated an Association between the Number of CMBs and the Symptoms

To get a large cohort, we took each hemisphere as two separate sides in all patients.

We observed 65 sides (46.4%) with ischemic symptoms (60 with strokes, 5 with cerebral TIAs) and 75 sides without ischemic symptoms. The prevalence of the CMBs was 42.8% (60/140).

Prevalence of CMBs was 61.53% in symptomatic sides. In asymptomatic sides, CMBs prevalence was 26.66%; a statistically significant difference between CMB presence was observed, with a P value of <0.0001 and an Odds ratio of 4.4 with 95% confidence interval of range 2.15 to 8.99.

3.2 Relationship of Plaque Type and CMBs

In the plaque type analysis of the 140 carotid arteries, we have 12 with no evidence of plaque (8.47%). In the remaining 128 carotid arteries, we found 100 fatty plaques (71.43%), 13 mixed plaques (9.29%), and 15 calcified plaques (10.71%).

In analyzing the relationship between CMBs and the type of plaque, we performed a correlation analysis and found a statistically significant direct correlation of CMBs with the fatty / soft plaques (correlation coefficient = 0.177; P value = 0.018). No statistically significant association was detected between CMBs and mixed plaque type (correlation coefficient 0.090; P value .145). Whereas an inverse statistical trend was observed between CMBs and calcified plaques (correlation coefficient 0.142; P value .047). For CMB having no evidence of plaques we found statistically significant inverse correlation of (correlation coefficient = 0.232; P value = 0.003).

3.3 ROC Curve Analysis

The ROC curve analysis for symptoms versus number of CMBs is shown in Fig. 1(a, b and c). The ROC area under the curve (AUC) was 0.7849. Using the ROC analysis, we calculated the sensitivity, specificity, positive likelihood ratio and negative likelihood ratio. A summary of these values is provided in Table 1. We also performed the ROC curve analysis for symptomatic (stroke and TIA) and asymptomatic patients, obtaining the following AUCs: 0.7849 and 0.6181 respectively. This confirms that there is an association between CMBs and symptoms but not between CMBs and asymptomatic patients.

4. DISCUSSION

Early histologic studies of patients with cerebrovascular disease revealed minor focal bleeds around abnormal cerebral small vessels, but with the advent of gradient-echo T2*-weighted MRI, it became a reality to observe these lesions in life. This technique is sensitive to paramagnetic (iron-containing) compounds including hemosiderin, which is a breakdown product of blood. Tiny areas of chronic bleed remain detectable for years as focal rounded hypointensities (“micro bleeds”) [12].

Micro bleeds predict future bleeding risk, such as aspirin-associated intracranial hemorrhage and hemorrhagic transformation after acute ischemic stroke.

Although micro bleeds have generally been considered to be clinically silent, they are associated with cognitive dysfunction [13,14].

The prevalence of CMBs in our study was 42.8% (60/140); which is significantly higher compared to results of recently published article by Saba et al. [15] (30%).This can be due to symptomatic target population and may be related to the ethnicity where eating habits are more prone towards fatty meals.

Our result is also higher compared with the prevalence of CMBs detected in Rotterdam Scan study (28%) and Vernooij et al. [16,17] (35.5%).

ROC curve analysis of CMB prevalence in the symptomatic versus asymptomatic side was 0.7849 and 0.6181 respectively, showing association of CMBs with cerebrovascular events (stroke/TIA). The results are similar to that of recent study by Saba et al. [15] and Ovbiagele et al. [18].

By analyzing the relationship between CMBs and the type of the plaque, we performed a correlation analysis and found a statistically significant direct correlation with the fatty / soft plaques (correlation coefficient = 0.177; P value = 0.018). No statistically significant association was detected between CMBs and mixed plaque type (correlation coefficient 0.090; P value .145). Whereas an inverse statistical trend was observed between CMBs and calcified plaques (correlation coefficient 0.142; P value .047). For CMB having no evidence of plaques, we found statistically significant inverse correlation. (correlation coefficient = 0.232; P value = 0.003). These results favour the cause of atherothrombotic stroke [19].

There are some limitations of our study. First, due to retrospective nature of the study, there was selection bias in subject population. Second, the prevalence of disease in our study is higher compared with the general population; this variability may be due to the heterogeneity of ischemic stroke per se, or to differences in recruited populations, rating strategies, and MRI parameters. Third, no interobsever variability was assessed and lastly, we did not emphasize on anatomical distribution of CMBs.

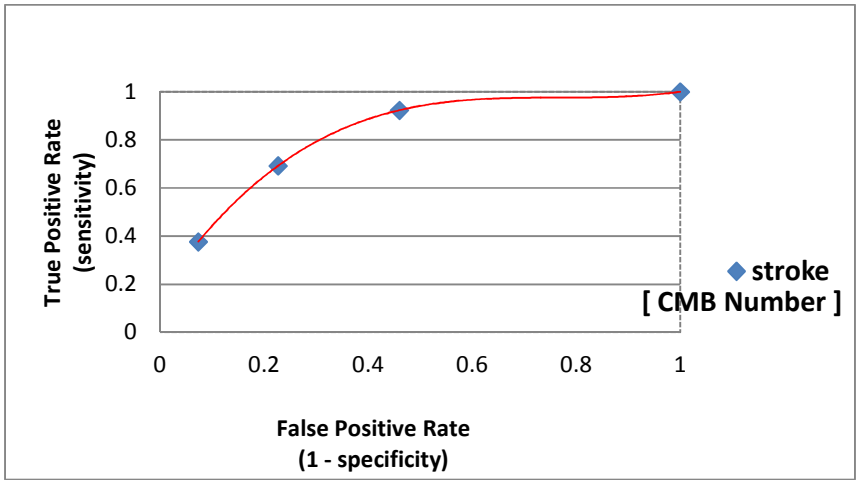

Fig. 1a

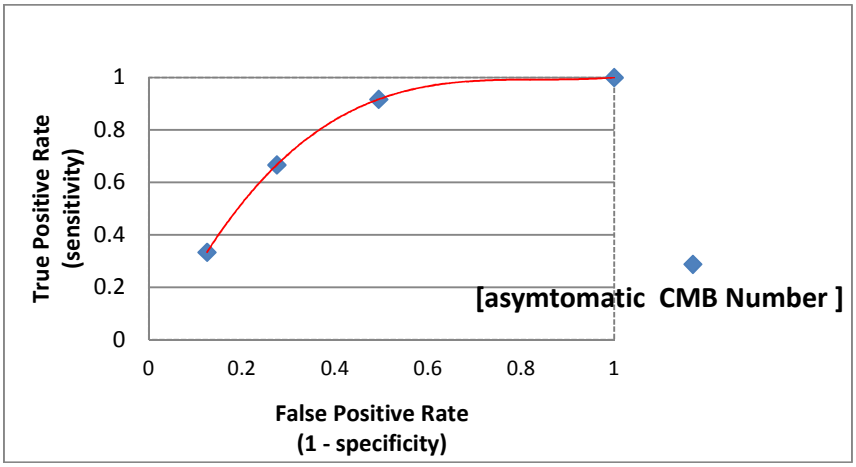

Fig. 1b

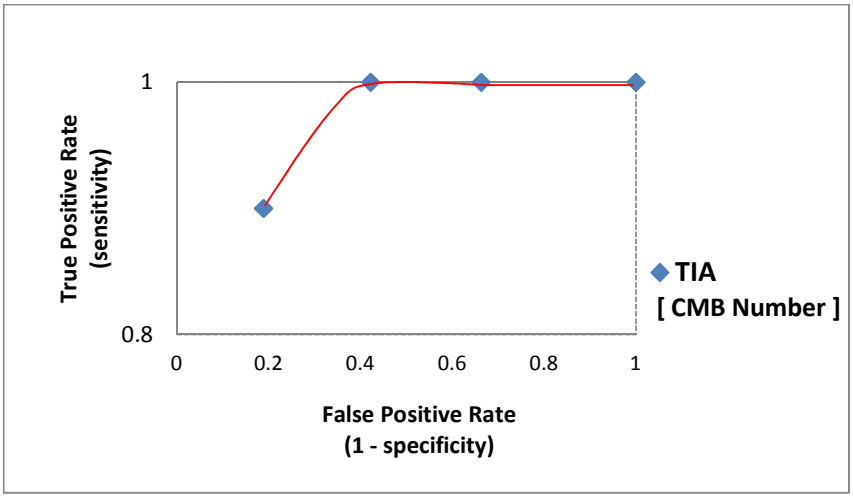

Fig. 1c

Fig. 1. The ROC curve analysis for symptoms versus number of CMBs

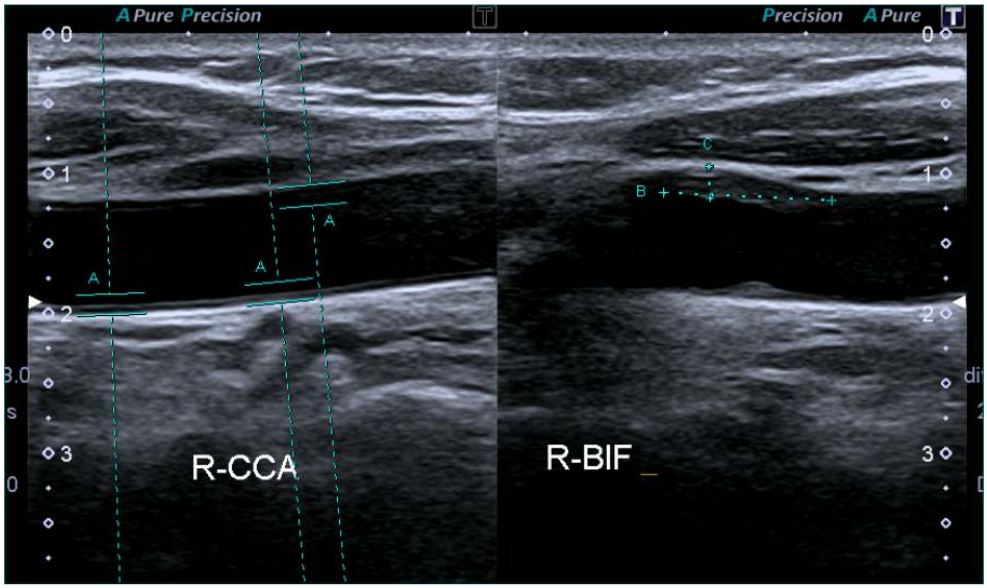

Fig. 2. Fifty year old, symptomatic patient who had a soft (fatty) plaque and acute right basal ganglia lacunar infarct with two chronic micro hemorrhages in the ipsilateral hemisphere

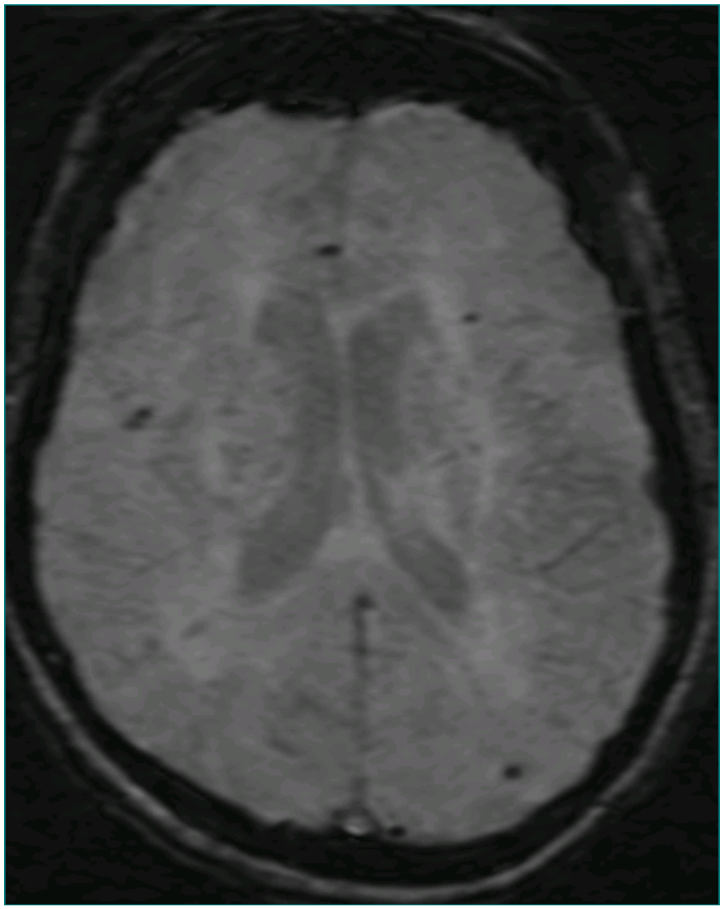

Fig. 3. A 6o year old female with risk factors of hypertension and diabetes was asymptomatic but had bilateral chronic micro-bleeds with calcified plaques in carotid bifurcations

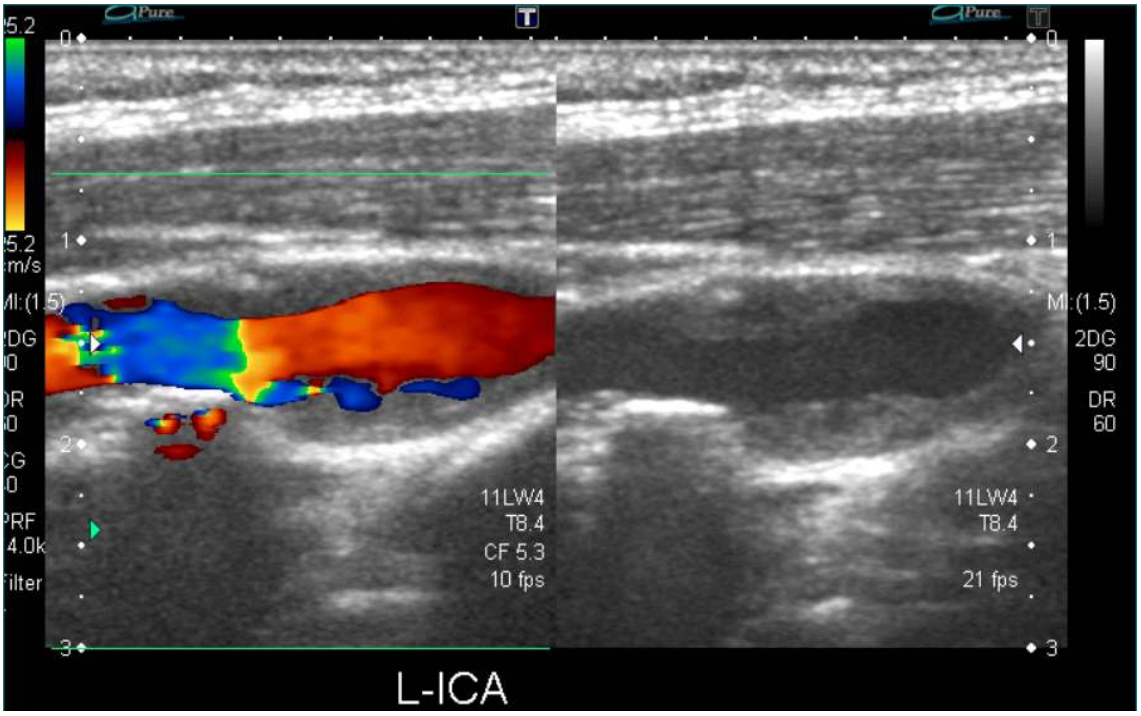

Fig. 4. A 75 year old diabetic male presented with acute left MCA territory infarct had a circumferential mixed plaque at the left proximal ICA

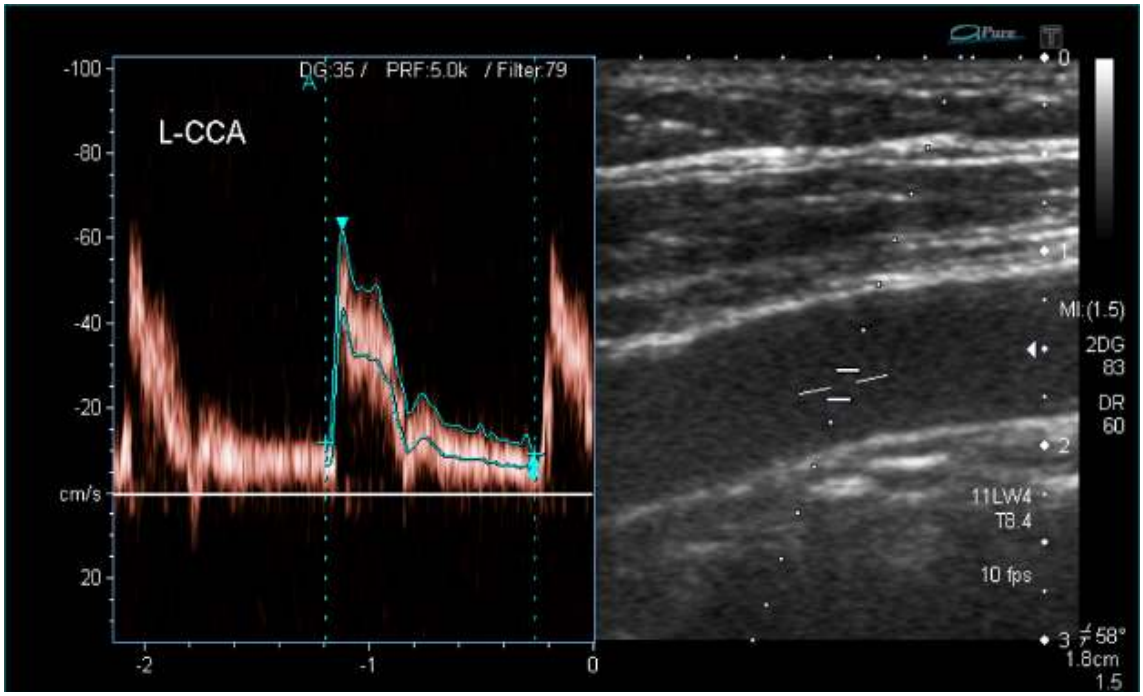

Fig. 5. A 50 year old male who had history of TIA underwent ultrasound carotid Doppler and had no plaque

Table 1. The ROC curve analysis for symptoms versus number of CMB. The table is showing further stratification in sensitivity, specificity, positive likelihood ratio and negative likelihood ratio

No. of CMB	Stroke		Asymptomatic		TIA	
	Yes	No	Yes	No	Yes	No
0	0.376923	0.073333	0.333333	0.125	0.9	0.188889
2	0.692308	0.226667	0.666667	0.275	1	0.422222
8	0.923077	0.46	0.916667	0.49375	1	0.662963
12	1	1	1	1	1	1

5. CONCLUSION

The study shows that there is a rising trend of chronic micro bleeds with fatty plaques. Moreover, chronic micro bleeds are prevalent in patients who have stroke or transient ischemic attacks.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Werring DJ, Coward LJ, Losseff NA, et al. Cerebral microbleeds are common in ischemic stroke but rare in TIA. Neurology. 2005;65:1914–18.
2. Werring DJ, Frazer DW, Coward LJ, et al. Cognitive dysfunction in patients with cerebral microbleeds on T2*-weighted gradient-echo MRI. Brain 2004;127:2265–75.
3. Wong KS, Chan YL, Liu JY, et al. Asymptomatic microbleeds as a risk factor for aspirin-associated intracerebral hemorrhages. Neurology. 2003;60:511–13.
4. Bos D, Ikram MA, Elias-Smale SE, et al. Calcification in major vessel beds relates to vascular brain disease. Arterioscler Thromb Vasc Biol. 2011;31:2331–37.
5. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: A call for new definitions and risk assessment strategies: Part II. Circulation. 2003;108:1772–78.
6. Wintermark M, Jawadi SS, Rapp JH, et al. High-resolution CT imaging of carotid artery atherosclerotic plaques. AJNR Am J Neuroradiol. 2008;29:875–82.
7. Saba L, Montisci R, Sanfilippo R, et al. Multidetector row CT of the brain and carotid artery: A correlative analysis. Clin Radiol. 2009;64:767–78.
8. Gaitini D1, Soudack M. Diagnosing carotid stenosis by doppler sonography: State of the art. J Ultrasound Med. 2005;24(8): 1127-36.
9. Rozie S, de Weert TT, de Monye´ C, et al. Atherosclerotic plaque volume and composition in symptomatic carotid arteries assessed with multidetector CT angiography; relationship with severity of stenosis and cardiovascular risk factors. Eur Radiol. 2009;19:2294–301.
10. Vit A, De Candia A, Piccoli G, Como G, Pelizzo F, Bazzaocchi M. Color-Doppler sonography vs CT-angiography in discriminating carotid atherosclerotic plaques for surgical treatment. A prospective study. Radiol Med. 2003; 106(4):382-90.
11. Reiter M, Horvat R, Puchner S, Rinner W, Polterauer P, Lammer J, Minar E, Bucek RA. Plaque imaging of the internal carotid artery - Correlation of B-flow imaging with histopathology. AJNR Am J Neuroradiol. 2007;28(1):122-6.
12. Pantoni L. Cerebral small vessel disease: From pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010;9:689–701.
13. Werring DJ, Frazer DW, Coward LJ, et al. Cognitive dysfunction in patients with cerebral microbleeds on T2*-weighted gradient-echo MRI. Brain. 2004;127:2265–75.
14. Cordonnier C, Al-Shahi SR, Wardlaw J. Spontaneous brain microbleeds: Systematic review, subgroup analyses and standards for study design and reporting. Brain. 2007;130:1988–2003.

15. Saba L, Montisci R, Raz E, Sanfilippo R, Suri JS, Piga M. Association between carotid artery plaque type and cerebral microbleeds. AJNR Am J Neuroradiol. 2012;33(11):2144-50.
16. Poels MM, Ikram MA, van der Lugt A, et al. Incidence of cerebral microbleeds in the general population: The Rotterdam Scan study. Stroke. 2011;42: 656–61.
17. Vernooij MW, Ikram MA, Wielopolski PA, et al. Cerebral microbleeds: Accelerated 3D T2*-weighted GRE MR imaging versus conventional 2D T2*-weighted GRE MR imaging for detection. Radiology. 2008; 248:272–77.
18. Ovbiagele B, Saver JL, Sanossian N, et al. Predictors of cerebral microbleeds in acute ischemic stroke and TIA patients. Cerebrovasc Dis. 2006;22:378–83.
19. Beom Joon Kima, Seung-Hoon Lee Cerebral microbleeds: Their associated factors, radiologic findings, and clinical implications. J Stroke. 2013;15(3):153–163.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/13551