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Cerebral Small Vessel Disease - Its Risk Factors and Effect of Risk Factor Management on Cognition

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Abstract: ***Background and Purpose: White matter lesions in the brain are linked to small vessel disease and have been connected to cognitive decline. Our goal was to examine how various risk factors, potential effect modifiers, and the progression of these lesions are related and to study risk factor modification on the cognition. Methods: 50 patients who fulfilled the inclusion and exclusion criteria, were evaluated for risk factors and their baseline cognition was assessed with Addenbrooke's Cognitive Examination (ACE) score, the risk factor modification was initiated and followed up at 3 months with repeat Addenbrooke's Cognitive Examination score, the relationship between lesion load, age, sex and cognitive function was assessed using multivariate regression analysis. Results: Severe white matter hyperintensities (WMH) were more prevalent in older age group, Hypertension, diabetes mellitus, smoking are independently associated with WMH. Fazekas grade and ACE scores were inversely related and there was no significant change in cognitive scores after 3 months of risk factor modification and follow up. Conclusion: Higher age, cigarette smoking, HTN, DM were independently associated with cerebral small vessel disease and there was no significant cognitive change after risk factor modification on follow up at 3 months.***

Keywords: Cerebral small vessel disease, Risk factors, Cognitive impairment

1. Introduction

Cerebral white matter lesions and lacunar brain infarcts are caused by cerebral small vessel disease. Narrowing of the small vessel lumen and failure of cerebral autoregulation result in ischemic damage. These lesions are commonly observed on MRI scans of elderly people and are associated with an increased risk of stroke, dementia, and depression, cognitive dysfunction. Hypertension is considered the main risk factor. Presence of small vessel disease - related lesions on MRI predicts cognitive decline. Studies in selected populations were too small to study modifiable risk factors for lesion progression. Data on risk factors, and the relation with cognitive function are essential in planning intervention studies. There is a need to have actionable data on the risk factors to identify modifiable risk factors if any and decrease the morbidity and disease burden in the population associated with small vessel disease. Hence we have undertaken this study to provide insights into the lacunae that are present in our understanding regarding these topics

2. Methods

1) **Study Design:** Observational Prospective Study
2) **Study subjects:** Patients diagnosed of cerebral small vessel disease by CT or MRI Brain
3) **Inclusion criteria:** All adults greater than 18 years of age with cerebral small vessel disease confirmed by neuroimaging are included in the study
4) **Exclusion criteria**
   - Recurrent stroke within study period
   - Dementia
   - Head trauma
   - Chronic Kidney Disease
   - Chronic liver disease
   - HIV
   - Psychiatric illness
   - Vit b12 deficiency
   - Demyelination
5) **Sample Size:** 50
6) **Period of study:** 24 months from date of approval
7) **Place of study:** Neurology, Medical wards and AMC of Tertiary care centre

Methodology

Patients fulfilling the inclusion and exclusion criteria were included in the study, with consent, blood investigations were done and Addenbrooke's Cognitive Examination (ACE) is done, and appropriate treatment for the risk factors was started, as per the standard guidelines. Patients were followed up for the next 3 months and they were subjected to ACE at 3 months, finding were noted and results were analyzed.

3. Results

Table 1: Age Distribution

Age interval years	Frequency	Percentage (%)
20 - 30	7	12
31 - 40	10	20
41 - 50	13	26
51 - 60	7	12
61 - 70	10	16
>70	3	4

largest age group in the sample is 41 - 50 years, which comprises 26% of the participants. Smallest age group is those over 70 years, which makes up 4% of the participants. The distribution shows a relatively balanced spread across other age groups, with each contributing between 12% and 20% to the total sample.

Table 2: Gender Distribution

Sex	No of Cases	Percentage
Male	13	26%
Female	37	74%
Total	50	100

In this study, the sample comprised 50 participants. Of these, 26% were male (n = 13), and 74% were female (n = 37), representing a total of 100% of the sample.

Table 3: Fazekas grade

Fazekas grade	N=50	%
1	21	42
2	19	38
3	10	20

The distribution of Fazekas grades in the sample of 50 participants was as follows: 42% were classified as Fazekas grade 1 (n = 21), 38% were classified as Fazekas grade 2 (n = 19), and 20% were classified as Fazekas grade 3 (n = 10)

Table 4: Distribution of Fazekas grading scale among different age

Fazekas grade	<50 years	>50 years
1	14	7
2	11	8
3	4	6

- In the younger group (<50 years), mild WMH (Grade 1) is most common.
- In the older group (>50 years), moderate WMH (Grade 2) is slightly more common than mild WMH (Grade 1).
- Severe WMH (Grade 3) is more prevalent in the older group (>50 years) compared to the younger group.

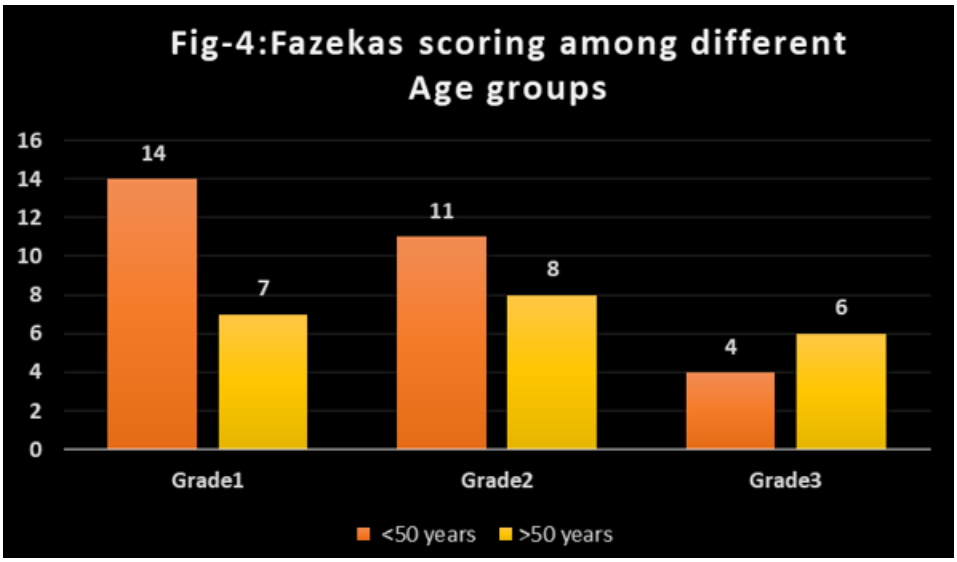

Figure 4: Fazekas scoring among different age groups

Table 5: Co - Morbidities among the cases

Co - Morbidity	Yes	No
HTN	38	12
DM	21	29
Hyperlipidaemia	6	44
Smoking	34	16
Alcohol	22	28

Hypertension (HTN): A significant majority (38) have hypertension, while a smaller group (12) do not.
Diabetes Mellitus (DM): Fewer individuals have diabetes (21) compared to those who do not (29).
Hyper lipidaemia: A very small number of individuals have hyperlipidaemia (6) compared to those who do not (44).
Smoking: There are a high number of smokers (34) compared to non - smokers (16).
Alcohol: There is a relatively even distribution between those who consume alcohol (22) and those who do not (28).

Hypertension and smoking are the most common comorbidities in this group. Hyper - lipidaemia is the least common comorbidity. Alcohol consumption is almost equally distributed between the two groups. The number of individuals with diabetes is slightly lower than those without diabetes.

Table 6: Fazekas scoring Correlation with Hypertension

Parameter	Value
Pearson correlation coefficient (r)	0.2834
r^2	0.08032
P - value	0.04845
Covariance	0.08971
Sample size (n)	50
Statistic	2.0261

Pearson correlation indicated that there is a significant small positive relationship between Fazekas grade and HTN,

Interpretation:
r=0.2834 indicates a small positive relationship. This means that as the Fazekas grade increases, more likely to have hypertension

Significance: The p - value of 0.04845 means this relationship is statistically significant at the 5% level, suggesting that the observed correlation is unlikely to be due to chance.

Proportion of Variance: The $r2$value of 0.08032 indicates that about 8% of the variance in Fazekas grades can be explained by hypertension. This is a relatively small proportion, meaning other factors likely play a larger role in determining Fazekas grades.

While the relationship between Fazekas grade and HTN is statistically significant, it is relatively weak (small positive correlation). This suggests that higher Fazekas grades are somewhat associated with the presence of hypertension, but many other factors also influence Fazekas grades.

Table 7: Fazekas scoring Correlation with Diabetes Mellitus

Parameter	Value
Pearson correlation coefficient (r)	0.3964
r^2	0.1571
P - value	0.00481
Covariance	0.1488
Sample size (n)	50
Statistic	2.9599

Pearson correlation indicated that there is a significant medium positive relationship between DM and Fazekas grade, r (47) =.396, p=.005.

Interpretation:

- Medium Positive Relationship: The correlation coefficient r=0.3964 indicates a medium positive relationship. This means that as the presence of diabetes increases, the Fazekas grade also tends to increase moderately.
- Significance: The p - value of 0.00481 means this relationship is statistically significant at the 1% level, suggesting that the observed correlation is highly unlikely to be due to chance.
- Proportion of Variance: The $r2$ value of 0.1571 indicates that about 15.71% of the variance in Fazekas grades can be explained by hypertension. While this is a moderate proportion, it also implies that other factors contribute to Fazekas grades.

The relationship between DM and Fazekas grade is statistically significant and medium in strength (medium positive correlation). This suggests that diabetes is moderately associated with higher Fazekas grades. However, other factors also play a role in determining Fazekas grades, as indicated by the $r2$ value.

Table 8: Fazekas scoring Correlation with Hyperlipidemia

Parameter	Value
Pearson correlation coefficient (r)	0.303
r^2	0.0919
P - value	p=0.034
Covariance	0.09269
Sample size (n)	50
Statistic	2.9599

Pearson correlation analysis was conducted to examine the relationship between Fazekas grade and hyperlipidemia among a sample of 50 participants. The analysis revealed a Pearson correlation coefficient of r=0.303, indicating a positive correlation between the two variables. This suggests that as Fazekas grade increases, the likelihood or severity of hyperlipidemia also tends to increase.

The r2 value of 0.0919 indicates that approximately 9.19% of the variance in hyperlipidemia can be explained by Fazekas grade. While this is a relatively small percentage, it indicate a meaningful relationship.

The significance level (p - value) for this correlation was p=0.034, which is less than the conventional threshold of 0.05. This means that the observed correlation is statistically significant, and the probability that this relationship is due to random chance is very low.

Additionally, the covariance between Fazekas grade and hyperlipidemia was 0.09269, further supporting the positive relationship between these variables.

In summary, results of this analysis suggest a significant medium positive relationship between Fazekas grade and hyperlipidemia in the sample studied, with higher Fazekas grades being associated with hyperlipidemia.

Table 9: Fazekas scoring Correlation with ACE levels at presentation

Parameter	Value
Pearson correlation coefficient (r)	0.736
r^2	0.5417
P - value	<.001
Covariance	- 7.5438
Sample size (n)	50
Statistic	2.9599

Results of the Pearson correlation indicated that there was a significant large negative relationship between Fazekas grade and ACE levels at presentation, r (47) = −.736

A Pearson correlation analysis was conducted to examine the relationship between Fazekas grade and ACE score at presentation among a sample of 50 participants. The analysis revealed a Pearson correlation coefficient of r=−0.736rv indicating a large negative correlation between the two variables. This suggests that as Fazekas grade increases, the ACE levels at presentation tend to decrease significantly.

The r2 value of 0.5417 indicates that approximately 54.17% of the variance in ACE levels at presentation can be explained by Fazekas grade. This is a substantial percentage, indicating a strong relationship.

The significance level (p - value) for this correlation was p<.001 (specifically, 1.681e - 9), which is well below the conventional threshold of 0.05. This means that the observed correlation is statistically significant, and the probability that this relationship is due to random chance is extremely low.

Additionally, the covariance between Fazekas grade and ACE levels at presentation was - 7.5438, further supporting the strong negative relationship between these variables.

In summary, results of this analysis suggest a significant large negative relationship between Fazekas grade and ACE levels at presentation in the sample studied, with higher Fazekas

grades being associated with lower ACE levels at presentation.

Table 10: Fazekas scoring Correlation with ACE levels after 3 months

Parameter	Value
Pearson correlation coefficient (r)	r=−0.7747
r^2	0.6002
P - value	<.001
Covariance	- 8.57
Sample size (n)	50
Statistic	- 8.3994

Results of the Pearson correlation indicated that there was a significant large negative relationship between Fazekas grade and ACE score at 3 months, r=−0.7747

Pearson correlation analysis was conducted to examine the relationship between Fazekas grade and ACE score at 3 months among a sample of 50 participants. The analysis revealed Pearson correlation coefficient of r=−0.7747, indicating a large negative correlation between the two variables. This suggests that as Fazekas grade increases, the ACE scores at 3 months tend to decrease significantly.

The $r2$ value of 0.6002 indicates that approximately 60.02% of the variance in ACE score at 3 months can be explained by Fazekas grade. This is a substantial percentage, indicating a strong relationship between these two variables.

The significance level (p - value) for this correlation was p<.001 (specifically, 6.498e - 11), which is well below the conventional threshold of 0.05. This means that the observed correlation is statistically significant, and the probability that this relationship is due to random chance is extremely low.

Additionally, the covariance between Fazekas grade and ACE score at 3 months was - 8.7857, further supporting the strong negative relationship between these variables. The test statistic for the correlation was - 8.3994, which reinforces the strength and significance of the relationship.

In summary, the results of this analysis suggest a significant large negative relationship between Fazekas grade and ACE score at 3 months in the sample studied. Higher Fazekas grades are associated with lower ACE scores at 3 months. This strong negative correlation implies that as the Fazekas grade increases, indicating more severe white matter changes, the ACE scores decrease correspondingly after 3 months.

Table 11: Comparison of ACE score at presentation and after 3 months

	MEAN	STD
Ace at presentation	73.40816327	13.65027
Ace after 3 months	71.85714286	15.10381
Difference	- 1.551	
Standard error	2.879	
95% CI	- 7.2645 to 4.1624	
t - statistic	- 0.539	
DF	98	
Significance level	P = 0.5913	

- The mean difference in ACE scores between the time of presentation and after three months is - 1.551, but this difference is not statistically significant.
- The wide confidence interval (-7.2645 to 4.1624) includes zero, reinforcing the lack of significant difference.
- The t - statistic of - 0.539, coupled with a p - value of 0.5913, further confirms that the change in ACE scores over three months is not statistically significant.

In conclusion, based on this statistical analysis, there is no strong evidence to suggest a significant change in ACE scores from the time of presentation to three months later after risk factor modification.

4. Discussion

Our study involved various age groups, with age between 41 - 50 years, being the largest age group. older age, hypertension, diabetes, hyper - lipideamia, smoking were the risk factors associated with presence of small vessel ischemic changes.

These risk factor were similar in previous studies carried out by Dijk Et All, Wahlund Et All (65), Xiong Et All (66), Brugulat Et All (67)

Hypertension was the most common risk factor in our study and is found in 76% of the patients, this was similar to other studies like Dobrynina et all where 84% had hypertension.

In our study Diabetes has been associated with increased risk of CSWD, the relation in other studies have been inconsistent (68, 69, 70)

Negative correlation was seen in our study between Fazekas score and ACE scores. Our study did not show significant reduction or improvement of cognitive impairment assessment by using ACE scores, after risk factor modification.

It is difficult to compare the distribution of white matter lesions between studies due to differences in study population, imaging techniques, lesion rating, lesion categorization, and risk factor distributions and the same holds for comparing progression of white matter lesions. (71) in the Austrian stroke prevention study, 18% of the participants had any and 8% had marked progression within 3 years of follow - up. (72)

In our study we did not find any change in cognition in 3 months of our follow up, the reason for it can be attributed to shorter duration of our study.

In cross - sectional studies, older age and higher blood pressure, in particular diastolic blood pressure, were strongly associated with WML severity.73, 74, 75. The Austrian Stroke Prevention Study And The Cardiovascular Health Study reported similar associations With age And blood Pressure. (76, 77) similar findings were seen also seen in our study.

Limitations of the study are

1) Duration of the study is short and it could impair our assessments.
2) The assessment of white matter lesions was semi - quantitative in nature, instead of volumetric analysis and has the possibility of under - estimating the lesions

Future implications from this study includes need to investigate risk factor modification over long duration and have a study to see for its effect and we need to emphasize the effect of risk factor modification on small vessel ischemic changes

The relationship between progression of small vessel disease and change in cognitive function is complex. a different kind of co - occurring lesion at a different anatomic location interacts in affecting different cognitive domains. despite this complexity, the relationship between periventricular WML progression and decrease in psychomotor speed seems robust given the comparable results in the cardiovascular health study and the prosper trial cohort. (77, 78, 79)

5. Conclusion

Cerebral small vessel disease is an entity associated with stroke, dementia and cognitive impairments, considering its prevalence, we need to be aware of the risk factors and also work to know the various associations of the risk factor with CSWD and also look for effects of risk factor modification to address the problems associated with it.

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