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Risk factors and consequences of enlarged Virchow Robin spaces in brain MRI scans

STUDENT RESEARCH

Risk Factors and Consequences of Enlarged Virchow Robin Spaces in Brain MRI scans

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Abstract

Virchow Robin spaces (VRS) are small areas of interstitial fluid that surround arteries and vessels in the brain parenchyma, according to MRI scans. It is hypothesized that enlarged VRS could result from vascular factors such as elevated blood pressure, or presence or absence of diabetes and in turn may be correlated with poorer cognitive function.

We assessed enlarged VRS from a subsample of 100 Framingham Study participants (mean age 78±13 years). The number of enlarged VRS rated on axial FLAIR images, across all slices, varied from 1-37. We also categorized the density of VRS based on the total count in each of two regions: basal ganglia and white matter. We used multivariate linear regression models, adjusted for age, sex and time between the assessment and MRI scan to relate systolic and diastolic blood pressure, presence or absences of diabetes (adjusting for anti-hypertensive medication) to number of VRS. We also related the number of VRS to performance on two cognitive tests (adjusting for education) assessing memory and executive functions, respectively.

We observed that 100% of our elderly sample had enlarged VRS (n=1270, mean 12.7±5.5 spaces). The sample size was too small to reliably arrive at statistically significant associations but we saw the following trends. For every 10 mm Hg rise in systolic blood pressure, the number of VRS decreased by 0.7, an unexpected inverse association. Diastolic Blood Pressure and presence or absence of diabetes was associated with a higher number of VRS, as expected. Scores on the Learning Memory Test improved as the number of VRS increased which was again unexpected. Scores on the Trails B Test fell as expected.

Introduction

Virchow-Robin spaces, also known as perivascular spaces are small quadrants of interstitial fluid that surround the arteries and veins near the parenchyma in the brain. As one ages, it has been noted that these spaces would often become enlarged or dilated. This significant increase in volume would allow them to become visible on MRI scans. At that time, these finding were not considered clinically significant. The observed dilation was attributed to age, blood pressure, and often inflammation.[1] However, more recent data suggests, while the presence of some spaces are normal, the presence of too many of them is likely to be abnormal with links to cerebral small vessel disease and/or Alzheimer's disease.[2] Individuals with abnormal blood pressure or increased stiffness of the arteries have been found likely to have enlarged Virchow-Robin spaces. After initial research in this field, many scientists are now of the opinion that the Virchow-Robin spaces could be used as a potential marker for the risk of stroke, cognitive impairment, dementia or even Alzheimer's disease.

With cognitive impairment and neurodegenerative disorders on the rise, a vast amount of time is being invested into researching these diseases, and determining markers and symptoms that could help us determine the risk of developing the disease many years before it actually arrives. One of these approaches includes determining whether the enlargement of Virchow-Robin spaces is indicative of the patient developing some form of cognitive disease. The data obtained by the Framingham Heart Study will be combined with information from other cohort studies such as the Rotterdam Study and the 3C Study. Each study retains data about the participants including whether or not they developed cognitive impairment or dementia in the 10 years after which they had their MRI taken.

One of the main issues that scientists researching Virchow Robin Spaces are facing is the development of a rating method that is not biased any population sample. Many demographic factors such as the age of the participant, and technical factors such as the quality of the MRI scan and the imaging sequences obtained may affect the number of enlarged VRS detected. Also a rating scale that is appropriate for a group of older persons with stroke may not be suitable for a group of younger, healthy

persons as it may have a 'floor' effect providing insufficient discrimination among persons with moderate numbers of enlarged VRS. This would be analogous to using an 8th grade science test to determine admission to medical school!

The overall aim of my research project was to examine if there was a positive correlation between the enlargement of Virchow-Robin spaces, and the probability of the onset of a neurodegenerative disease, dementia or a cognitive impairment in that individual. This probability was measured using two different cognitive function tests; the Learning Memory Test and the Trail B test. I also aimed to study risk factors for enlarged VRS and hypothesized that we would observe a positive correlation between elevated systolic or diastolic blood pressure and presence or absence of diabetes and a greater number of enlarged VRS. Using a method for rating Virchow Robin Spaces derived by researchers at Massachusetts General Hospital, I simultaneously attempted to validate this particular rating method for our population sample. For this purpose, I read 100 MRI scans and analyzed them for the presence of Virchow-Robin spaces.

A validation of the above hypothesis would support already published data regarding Virchow-Robin Spaces and systolic blood pressure along with cognitive impairment, allowing us to ensure the rating method used in this project was accurate for our sample. It would also show that the correlation between these factors is clinically significant as it was prominent even in a small sample.

Anna / Thompson / of South / Boston / employed / as a cook / in a school / cafeteria / reported / at the police / station / that she had been held up / on State Street / the night before / and robbed of / fifty-six dollars. / She had four / small children / the rent was due / and they hadn't eaten / for two days. / The police / touched by the woman's story / took up a collection / for her.

Figure 1: Logical Memory Test: A sample of Story A that is read to the participant during the administration of this test.

Methods

Study Participants

Originally, 5,209 participants were enrolled into what is termed as the "Original Cohort". Following this in 1971, 5,124 participants (offspring of those who participated in the Original Cohort) were enrolled into the "Offspring Cohort". From March of 1999 to November of 2004, 2,905 participants received an MRI scan of their brain. A second MRI was given to 1,971 of the participants who have received a first MRI, between January of 2005 and August of 2011. The "3rd Generation Cohort" began in 2000, and between June of 2009 and March of 2013, 2,008 participants had received an MRI scan. At this point, a total of 8,100 image sets have between collected amongst the three cohort studies.

Study Design

Systolic and Diastolic Blood Pressure and Presence/Absence of Diabetes:

Each participant had a complete physical check-up conducted as a part of this study. A part of this check-up included a clinician who measured the systolic and diastolic pressure for the individual in the right arm in a seated posture; the average of the two readings was taken. This was conducted using a Clinical Mercury Sphygmomanometer and blood pressure was measured in mm Hg. The clinician also confirmed with the participant, whether they had diabetes based on fasting blood sugar (or 2 hour postprandial blood sugar) or use of a diabetes treatment medication such as insulin.

Cognitive Function Tests

Learning Memory Test:

The objective of this test is to give the participant more information than an individual can normally remember, and note how much the participant is able to recall. Two stories are read to the participant, Story A and Story B. Each story has 25 ideas that can be potentially recalled. The doctor or neuropsychologist conducting the neuropsychological evaluation first tests the recall immediately after reading the story, and then again 20-30 minutes later, known as a delayed recall. The participant gets 1 point for each idea correctly recalled. The total score is the average of the score of both tests.

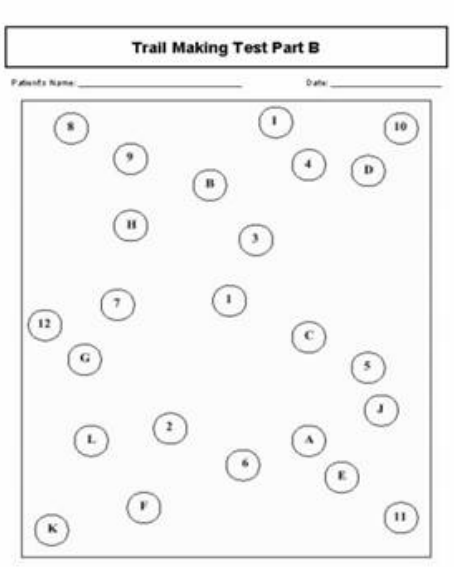

Figure 2: Trail B Test: A copy of the sheet given to the participant for the completion of this test. The participant is asked to draw a line from a number to a letter (1-A-2-B) till all of the circles are connected.

Trail B Test:

The participant is given a sheet of paper with 25 circles. The circles contain the numbers 1-13 and the letters A-L. The objective of the task is to draw a line connecting the circles in an alternating pattern of number, letter, number, letter, etc. The participant is timed while they complete the task. The average person would complete the task in about 75 seconds. Cognitive deficiency becomes a factor when the participant is taking more than 273 seconds. If the participant takes more than 300 seconds, they are stopped and given the lowest score possible.

MRI's:

One hundred MRI scans obtained on a 1.5T machine were utilized; we evaluated the FLAIR sequence images. The particular scans that were read came from the 1st and 2nd

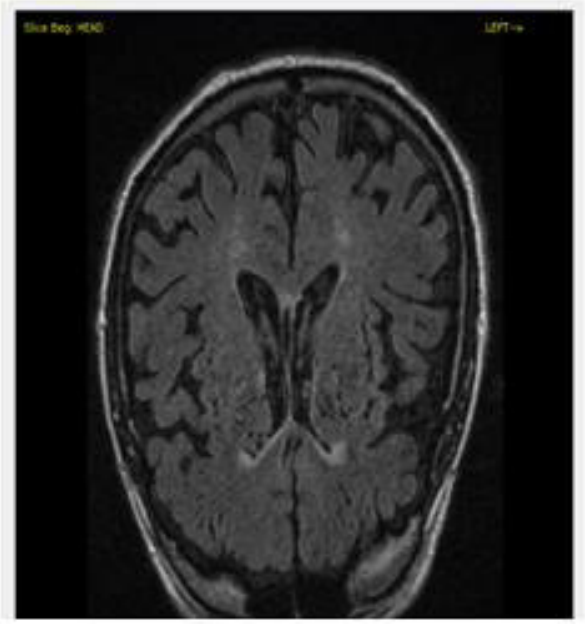

Figure 3: FLAIR Image of MRI scan of a patient with enlarged Virchow-Robin Spaces. Such a high presence is abnormal.

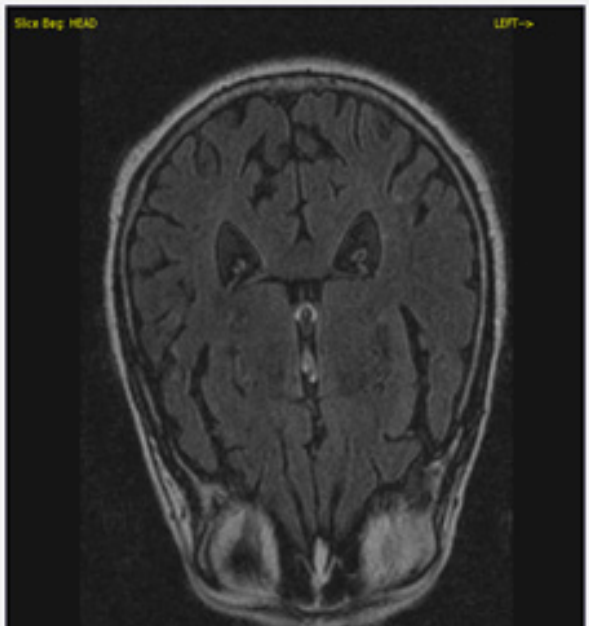

Figure 4: FLAIR Image of an MRI scan of a patient with enlarged Virchow-Robin Spaces. Presence of some spaces is normal particularly in participants of the Original Cohort (1948).

generation participants of the Framingham Heart Study, a longitudinal cohort study that began in 1948 with the aim of investigating the various risk factors for cardiovascular diseases. This cohort study is made up of three generations of residents from Framingham, MA.

Rating System

The rating system used in this project was described by neurologists and radiologists at Massachusetts General Hospital. This method rates enlarged spaces based on the degree of severity in two separate regions; the basal ganglia and white matter.

Statistical Analysis

A multivariate linear regression model was used to analyze the given data.

Systolic and Diastolic Blood Pressure

Of the 100 participants whose MRI scans were read, only 93 were used. This was because one of the MRI scans was a duplicate and 6 participants did not have an exam with Systolic Blood Pressure within 5 years before the MRI scan was taken. For these analyses we adjusted for age, sex, time between clinic exam and MRI, and antihypertensive medication.

Presence or Absence of Diabetes

Of the 100 participants whose MRI scans were read, only 85 were used for this analysis. This was because one of the MRI scans was a duplicate and 14 participants did not have an exam within 5 years before the MRI scan was taken. For this analysis we adjusted for age, time between clinical exam and MRI, and hypertensive medication.

Cognitive Function Test

Of the 100 participants whose MRI scans were read, 96 were used for the Learning Memory Test and 90 were used for the Trails B Test. This was because one of the MRI scans was a duplicate and the others did not have a cognitive function test within 1 year before the MRI scan was taken. For this analysis we adjusted for age, sex, education and time between the neuropsychological evaluation and the MRI.

Discussion

It is to be noted that the sample size used in this project was too small for the results to be considered statistically significant. We saw the expected correlation with three of our factors which included diastolic blood pressure, presence/absence of diabetes and the Trail B Cognitive Functioning test, and an inverse association for the others; systolic blood pressure and the Learning Memory Cognitive Function test. From our results we believe there may have been two issues that may have contributed to the inaccuracy of our data. The first would be the rating system. The rating system we used for this project was developed by researchers who were reading scan of hospitalized patients. As our participants came from a healthy population, this method may not be the most accurate system to use. Another factor that could have played a role was the mean age of our sample. The scans I read for this project came mostly from the 1st and 2nd generation participants and the entire sample had a mean age of 78 years. As our sample was more towards the older end of the age scale, we may have been including some bias in our data regarding conditions they may have developed due to aging. We plan on re-evaluating the data using a larger data sample spread across all three generations, as well as a more accurate rating system and is geared toward our study population.

Acknowledgment

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Location and Degree of Severity	Number of Deep Perivascular Spaces (DPVS)
Basal Ganglia – 1	< 5 DPVS
Basal Ganglia – 2	5-10 DPVS
Basal Ganglia – 3	10 but finite DPVS
Basal Ganglia – 4	Innumerable DPVS
White Matter – 1	< 10 DPVS
White Matter – 2	> 10 DPVS in total and < 10 in the slice containing the most DPVS
White Matter – 3	10 – 20 DPVS in the slice containing the most DPVS
White Matter – 4	> 20 DPVS in the slice containing the most DPVS

Table 1: Rating Parameters: A summarization of the rating method used to rate MRI scans in this project. Ratings were assigned based on the degree of severity.

Rating Area and Degree	Number with outcome/Total sample	OR [CI] for increase of 1 unit of DBP	Probability
DPVS ≥ 1	9/93	0.99 [0.91-1.08]	0.816
DPVS ≥ 2	4/93	1.12 [0.96-1.31]	0.157
WMPVS ≥ 1	66/93	0.99 [0.94-1.04]	0.641
WMPVS ≥ 2	4/93	1.12 [0.96-1.31]	0.157
Combined ≥ 2	67/93	0.98 [0.93-1.03]	0.474
Combined ≥ 3	8/93	1.01 [0.92-1.10]	0.903

Table 3: Diastolic Blood Pressure: Correlation between Diastolic Blood Pressure and Virchow-Robin Spaces. We saw in increase in Virchow-Robin Spaces associated with this factor.

Rating Area and Degree	Learning Memory Test: beta [se]	Learning Memory Test: Probability (p-value)	Trail B: beta [se]	Trail B: Probability (p-value)
DPVS ≥ 1	0.29 [1.67]	0.864	-0.16 [0.16]	0.305
DPVS ≥ 2	0.49 [2.44]	0.841	-0.43 [0.23]	0.062
WMPVS ≥ 1	3.61 [1.01]	<0.001	0.21 [0.09]	0.025
WMPVS ≥ 2	0.49 [2.44]	0.841	-0.43 [0.23]	0.062
Combined ≥ 2	3.55 [1.03]	<0.001	0.17 [0.10]	0.074
Combined ≥ 3	0.84 [1.82]	0.644	-0.05 [0.17]	0.770

Table 5: Cognitive Function Test: Correlation between Cognitive Function Test and Virchow-Robin Spaces. We saw an increase in Virchow-Robin Spaces as scores on the Trail B Test decreased, but an increase in spaces as scores increased on the Logical Memory Test.

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Rating Area and Degree	Number with outcome/Total sample	OR [CI] for increase of 1 unit of SBP	Probability
DPVS ≥ 1	9/93	0.96 [0.91-1.00]	0.060
DPVS ≥ 2	4/93	0.99 [0.93-1.05]	0.767
WMPVS ≥ 1	66/93	0.97 [0.94-1.00]	0.030
WMPVS ≥ 2	4/93	0.99 [0.93-1.05]	0.767
Combined ≥ 2	67/93	0.97 [0.94-0.99]	0.020
Combined ≥ 3	8/93	0.96 [0.91-1.00]	0.075

Table 2: Systolic Blood Pressure: Correlation between Systolic Blood Pressure and Virchow-Robin Spaces. We saw a decrease in Virchow-Robin Spaces by 0.7, for every 10 mm Hg rise in blood pressure.

Rating Area and Degree	Number with outcome/Total sample	OR [CI] for Diabetes	Probability (p-value)
DPVS ≥ 1	7/85	3.64 [0.24-54.82]	0.351
DPVS ≥ 2	4/85	---	---
WMPVS ≥ 1	63/85	1.47 [0.25-8.46]	0.670
WMPVS ≥ 2	4/85	---	---
Combined ≥ 2	64/85	3.41 [0.37-31.21]	0.278
Combined ≥ 3	6/85	---	---

Table 4: Presence or Absence of Diabetes: Correlation between Diabetes and Virchow-Robin Spaces. We saw an increase in Virchow-Robin Spaces associated with this factor.

Nikita is a junior studying Neuroscience and Psychology, with a special interest in dementia and potential biological markers. After graduating from BU, she plans on pursuing a career in medicine as a Neurologist.