Interplay between Infarction Volume and Location to Mediate the Occurrence of Vertigo in patients with Vertebrobasilar Stroke

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Ahmed Mohamed Elhfnawy
Universitatsklinikum Wurzburg

Ahmedmelhfnawy@gmx.de*Corresponding Author*
ORCiD: https://orcid.org/0000-0001-9800-7830

Doaa Elsalamawy
Alexandria University Faculty of Medicine

Jens Volkmann
Universitatsklinikum Wurzburg

Felix Fluri
Kantonsspital St Gallen

Mervat Abd El-Raouf
Alexandria University Faculty of Medicine

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Abstract

Background

Vertigo is a common presentation of cerebellar or dorsal brain stem infarctions. However, the relation between infarction volume and the development of vertigo in patients with vertebrobasilar stroke was never investigated. In this study, we aimed to examine the interaction between the infarction size and location on the development of vertigo in patients with vertebrobasilar stroke.

Methods

Fifty-nine consecutive patients presenting with vertebrobasilar stroke were recruited and stratified into the presence or absence of vertigo. National institute of health stroke scale (NIHSS) on admission as well as modified Rankin Scale (mRS) and Barthel-index on discharge were used as clinical scales. The infarction location and volume were assessed in the diffusion-weighted images of magnetic resonance imaging (MRI).

Results

The infarction volume did not correlate with NIHSS-score on admission (ρ=0.077, p=0.56) but correlated with mRS (Spearman ρ=0.37, p=0.004) and Barthel index on discharge (ρ=0.33, p=0.011), serum levels of HbA1c (ρ=0.3, p=0.02) as well as white blood cells (ρ=0.34, p=0.008). Patients with vertigo had less male predominance (53.1% versus 77.8%, p=0.049) and were less likely to have focal neurological manifestations (65.6% versus 96.3%, p=0.004) in comparison to those without vertigo. The median of the total infarction volumes were statistically significant larger among patients with vertigo (5.6 versus 0.42 cm3, p=0.008). In an age and sex adjusted multivariate binary logistic regression model, an infarction location either in the cerebellum or dorsal midbrain and a total infarction volume of >0.48 cm3 were found to have an OR (95% CI) of 16.97 (3.1-92.95), p=0.001 and 4.4 (1.05-18.58), p=0.043, respectively to be associated with vertigo.

Conclusion

In addition to the infarction location in the cerebellum and/or dorsal brain stem, it seems that the infarction volume plays a role in the development of vertigo among patients with vertebrobasilar stroke. In patients with vertebrobasilar stroke, increased serum levels of HbA1c and leukocytosis

seems to mediate the development of large infarctions.

Background

Dizziness is a major public health problem with an annual incidence of 11% and is associated with 2.2 times increased mortality [1]. Dizziness and vertigo are more common among women and elderly population [2, 3]. Affected patients do not usually receive the adequate medical management and are more likely to consult a general practitioner or an internist rather than a neurologist or an ear, nose and throat specialist [3]. Stroke is the underlying etiology in 17-25% and 4% of patients presenting with acute onset isolated vertigo [4, 5] and dizziness [6], respectively. Of note, 18.9% of patients with vertebrobasilar stroke suffer from vertigo in comparison to only 1.7% of those with stroke in the anterior circulation [7]. Lesions affecting the following structures are related to the development of vascular vertigo: vestibular nuclei in the dorsolateral portion of the rostral medulla, nucleus prepositus hypoglossi in the dorsal brainstem, dorsal insular cortex as well as cerebellar tonsil, flocculus, nodulus and inferior cerebellar peduncles [2, 3, 8-11]. However, to our knowledge, the relation between infarction volume and the development of vascular vertigo has never been studied. In this work, we aimed to examine a relation exists between the infarction volume and the development of vascular vertigo among patients with vertebrobasilar stroke.

Methods

Fifty-nine consecutive patients admitted to the Department of Neurology (University Hospital of Würzburg) with the diagnosis of vertebrobasilar stroke were prospectively recruited between February and October 2018. Patients were included only if they could communicate the presence or absence of vertigo and a magnetic resonance imaging (MRI) could be done within 4 days of admission and showed brain infarction. Patients were excluded, if the infarction was located mainly in the anterior circulation. National institute of health stroke scale (NIHSS) on admission as well as modified Rankin Scale (mRS) and Barthel-index on discharge were used as clinical scales. Patients were stratified into two groups: group 1 with vertigo (vertigo +) and group 2 without vertigo (vertigo -). Focal neurological manifestations were deemed to be present, if a localization to one cerebral hemisphere was possible. This included patients with aphasia, hemi- or quadrantanopsia as well as lateralized

motor weakness, ataxia or sensory symptoms.

MRI imaging:

MRI scanners with a field strength of 3 Tesla were used according to standardized acquisition protocols with a slice thickness of 5 mm and an interslice gap of 0.5 mm. The infarction location and volume were assessed in the strong (b=1000) diffusion weighted images (DWI) by a senior stroke neurologist with vascular neuroradiology background (AME), who was non-blinded to the clinical data. The infarction area was measured in each slice separately and was multiplied by the slice thickness and interslice gap. Finally, the sum of all slices was calculated to obtain the infarction volume [12, 13].

Statistical analyses:

Qualitative data were expressed in absolute values and percentages, while quantitative data were expressed using median and range. To check for normality, we used QQ-plot, histogram and the Shapiro-Wilk test. Univariate statistical tests were conducted for categorical data using $\chi 2$ test and if $n<5$, Fisher's exact test was used. For continuous data, we used the Mann-Whitney U-test. Spearman coefficient was used to analyze correlations. To calculate the cut-off infarction volume value for the occurrence of vertigo, a receiver operating curve (ROC) was used. Univariate binary logistic regression analysis was performed to measure the strength of association, measured as OR (95%CI), between the occurrence of vertigo and other possibly related variables. To adjust for age and sex, we conducted a multivariate logistic regression with inclusion method. In this model, we included variables found in the univariate model with $p<0.1$. Data were analyzed in SPSS software package version 25 (SPSS, Chicago, IL, USA). P-values <0.05 were considered statistically significant.

Results

Five-hundred and forty-six (546) patients were screened, of whom 59 were included in the study. Baseline characteristics are illustrated in Table 1. There was a statistically significant less male predominance among vertigo (+) patients in comparison to vertigo (-) patients (53.1% versus 77.8%, respectively, $p=0.049$). Otherwise, no statistically significant difference was found between the baseline characteristics of the two groups. Vertigo (+) patients were statistically significantly more

likely to present without focal neurological manifestations (34.4% versus 3.7%, respectively, p=0.004) and had a “borderline” statistically significantly delayed presentation with a median time from symptom onset to presentation of 7.5 versus 4 hours (p=0.052), respectively, in comparison to vertigo (-) patients. An infarction location either in the cerebellum or in the dorsal brain stem was obviously more common among vertigo (+) patients in comparison to vertigo (-) patients (90.6% versus 40.7%, respectively, p<0.001). The total infarction volume was statistically significantly larger among vertigo (+) patients with a median of 5.6 versus 0.42 cm3 among vertigo (-) patients (p=0.008, Figure 1.A). This difference was even more evident for infarctions located in the cerebellum with a median of 9.09 versus 0.26 cm3 for vertigo (+) patients in comparison vertigo (-) patients, respectively. Figures 2 and 3 show different examples for patients with vertigo (+) and vertigo (-) patients with vertebrobasilar stroke.

Using a ROC-curve, a volume of >0.48 cm3 for all infarctions and a volume of >0.36 cm3 for infarctions located in the cerebellum was found to have a sensitivity of 84% and 96% as well as a specificity of 56% and 78%, respectively to be associated with vertigo. In an age and sex adjusted multivariate binary logistic regression analysis, an infarction location either in the cerebellum or dorsal midbrain and an infarction volume of >0.48 cm3 were found to have an OR (95% CI) of 16.97 (3.1-92.95), p=0.001 and 4.4 (1.05-18.58), p=0.043, respectively to be associated with vertigo (Table 2).

We found a statistically significant positive correlation between the infarction volume and the serum levels of HbA1c (Spearman, ρ=0.3, p=0.02) as well as white blood cells (ρ=0.34, p=0.008). A tendency for a positive correlation was observed between the total infarction volume and erythrocyte sedimentation rate (ρ=0.24, p=0.077) but not C-reactive protein (ρ=0.2, p=0.135). The median (IQR) infarction volume among women was 3.99 (0.92-26.86) cm3 versus 2.32 (0.21-12.35) cm3 among men (p=0.11, Figure 1.B) and among hypertensive patients was 4.74 (0.3-17.28) versus 1.69 (0.19-3.99) cm3 among non-hypertensive patients (p=0.11). The correlation between the infarction volume and age was ρ=0.21 (p=0.1). We observed no correlation between infarction volume and serum levels of LDL-cholesterol (Spearman ρ=0.00, p=1.0, n=59) and no relation between infarction volume

and smoking (p=0.99).

The total infarction volume did not correlate with NIHSS-score on admission (ρ=0.077, p=0.56) but correlated with mRS as well as Barthel index on discharge (ρ=0.37, p=0.004 and ρ=0.33, p=0.011, respectively).

Discussion

We found that vertigo (+) patients had less male predominance, larger infarction volume and were less likely to have focal neurological manifestations in comparison to vertigo (-) patients. Similar to previous authors [2, 3, 8-11], we found that an infarction location in the cerebellum or dorsal brain stem was very strongly related to the development of vertigo. Moreover, the infarction volume, especially for cerebellar infarction, was evidently related to the occurrence of vertigo among our patients. To our knowledge, no similar reports exist in literature. We speculate that larger infarcts, especially in the cerebellum, mediate the development of vascular vertigo through affection of several brain structures and interconnections. Similar to our results, previous authors identified small lesions ≤ 10 mm in axial diameter in only 14% of patients with vascular vertigo [11]. The authors found focal neurological signs among 27% of their patients with small lesions, whereby the inferior cerebellar peduncle and the lateral medulla were most often involved.

The incidence of stroke in men is 32% higher than in women [14]. Furthermore, the odds ratio for the development of vertebrobasilar stroke rather than stroke in the anterior circulation was even found to be higher among men [15]. Contrarily, men represent around one-third of the vertigo population [2, 3]. In our cohort, we found less male predominance among vertigo (+) stroke patients in comparison vertigo (-) stroke patients. It might be speculated that females were more prone to develop vascular vertigo and hence the male percentage among our vertigo (+) stroke patients was diluted. In line with our findings, previous authors found male percentage of 55-57% among patients with acute vascular vertigo [4, 9]. In the current work, the infarction volume was statistically insignificantly larger among women. In other terms, the female sex predisposed to vascular vertigo and might be related to the development of larger infarcts. Previous authors found a median infarction volume, assessed using computer tomography, of 79.4 in women versus 29 cm3 in men (p=0.15) among stroke patients with

non-valvular atrial fibrillation. Similarly, another study showed a negative statistically insignificant association between male sex and infarction volume in the anterior circulation (p=0.147) [16]. In our cohort, the median infarction volume among women was 3.99 cm3 versus 2.32 cm3 among men (p=0.11). Conversely, in experimental stroke models, female rats experienced smaller infarction volume in the middle cerebral artery as compared to males, whereas ovariectomized rats experienced similar infarction volumes to male rats [17].

We found a “borderline” statistically significant tendency for vertigo (+) patients to have a delayed presentation in comparison to vertigo (-) patients. This can be attributed to less predominance of focal neurological manifestations among vertigo (+) patients. In line with these findings, other authors showed that 37% of patients with vertebrobasilar stroke versus 16% of patients with stroke in anterior circulation were misdiagnosed (p<0.001) and the presence of focal neurological signs helped to pave the way for the accurate diagnosis [18]. In a previous cohort, only 42% of patients with vertebrobasilar stroke presenting with vertigo had obvious neurological signs [8]. In the current cohort, 65.6% of patients with vascular vertigo had focal neurological manifestations.

NIHSS score is lower among patients with vertebrobasilar stroke in comparison to those with stroke in the anterior circulation [19-21]. This can be explained by the fact that several clinical manifestations related to the posterior circulation like vertigo, nystagmus, nausea or vomiting are not considered in NIHSS [4], but may lead to a worse score on mRS or Barthel index. For example, a patient with vertebrobasilar stroke presenting with severe vertigo and nystagmus may have an NIHSS-score of 0 but a mRS-score of 3, if he requires some help for the activities of daily living. In our cohort, the infarction volume did not correlate with NIHSS-score on admission but correlated with mRS and Barthel-index on discharge.

Historically, the World Health Organisation (WHO) defined transient ischemic attack (TIA) as a transient focal neurological deficit lasting less than 24 hours [22]. This definition was introduced in the 1960s, at the time when magnetic resonance imaging (MRI) was not yet invented. Later on, it was found that 30-50% of patients with this classical TIA definition do have brain infarctions on MRI [23-25]. In 2009, the American Heart Association/American Stroke Association (AHA/ASA) revised the

historical TIA definition, stating that a TIA is “a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction” [23]. The implementation of this AHA/ASA definition “moved” a significant proportion of patients from the TIA to the stroke category [26]. In the current work, 12/59 (20.3%) of the patients had no focal neurological manifestations, yet they had a brain infarction on MRI. In other words, those patients corresponded to the old TIA definition of the WHO but to the modern AHA/ASA stroke definition.

We found a positive association between the infarction volume and the serum levels of HbA1c. Previous authors found larger infarction volumes in the anterior circulation in patients with higher serum levels of HbA1c [16]. In another study, the infarction volume was found to be largest in patients with high-risk cardioembolic infarction, followed by infarctions on top of internal carotid artery occlusion and smallest in patients with medium-risk cardioembolic infarction and in patients with internal carotid artery stenosis [13]. Of note, male sex and diabetes were statistically significantly different between the four study groups (male sex: 52%, 77.3%, 84% and 63.6%, $p=0.009$ and diabetes: 19.4%, 13.6%, 40% and 40.9%, $p=0.029$, respectively). Whether, diabetes and female sex, in the aforementioned cohort and possibly in our study potentiated the development of larger infarctions remains a subject for future research.

Inflammation is increasingly recognized to have a potential pathophysiological mechanism in ischemic stroke [27]. Previous authors found a positive relation between polymorphonuclear leucocytes accumulation in brain infarction, assessed using single-photon emission tomography, and infarction volume in patients with middle cerebral artery infarction [28]. In our patients, a statistically significant correlation was found between serum levels of white blood cells and the infarction volume. We did not find similar reports in the literature.

There are several limitations in this study. The variability of time between symptom onset and MRI is a drawback for this study. However, this time was slightly greater in patients with vertigo, who were also found to have larger infarction volume. In order to minimize this drawback, we included patients, who underwent MRI imaging within 4 days of symptom onset. Although a non-blinded examiner (AME) assessed the images, we do not think that the non-blindness influenced our results. The

dichotomization of our patients according to the presence or absence of vertigo was not initially planned and was done first after the impressive statistical results. The non-randomized nature of our relatively small cohort should be kept in mind before a conclusion can be drawn. The good NIHSS scores of our cohort may partially related to a selection bias, whereby patients, who were able to communicate the presence or absence of vertigo, were selected.

Conclusion

In the current cohort, we found that vertebrobasilar stroke patients with vertigo had less male predominance, larger infarction volume and were less likely to have focal neurological manifestations in comparison to those without vertigo. It seems that the development of vascular vertigo is mediated not only by the location of the brain infarction in the cerebellum and/or dorsal brain stem but also by the infarction volume. The latter might be mediated through affection of brain connections. However, such a hypothesis has to be investigated in future research. Serum levels of HbA1c as well as leukocytosis are apparently positively related to the infarction volume among patients with vertebrobasilar stroke.

List Of Abbreviations

Diffusion weighted images (DWI)

Modified Rankin Scale (mRS)

National institute of health stroke scale (NIHSS)

Receiver operating curve (ROC)

Transient ischemic attack (TIA)

World Health Organisation (WHO)

Declarations

Ethics approval and consent to participate

Data collected within routine clinical care were used. The study was approved from the University Hospital Würzburg Ethics Committee (AZ 223/16). The study doctor informed the patient in details about the study design and the patient was given a reasonable time to consider his willingness for approval to participate in the study and finally signed a written informed consent. If the patient had no power of attorney, the legal representative or, if not available, the next available relative signed

the written informed consent. This recruitment process is in accordance with the local regulations of our Ethics Board and was approved from our Ethics Committee.

Consent for publication

Not related.

Availability of data and materials

The dataset of the current study is available from the corresponding author upon reasonable request.

Competing interests

None

Funding

None

Authors’ contributions

All authors made substantial contribution to the conception, design and revision of the work. MAE and/or FF examined all the patients. AME collected the data, performed the measurements and the statistical analysis and wrote the first draft. DE, MAE, JV and FF supervised the work, provided consultations and revised the manuscript. All authors were involved in the final approval of the version to be published.

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Tables

Table 1: Baseline characteristics

Characteristic	Vertigo (-), n=27	Vertigo (+), n=32	P-value
Age in years	66 (55-77)	70 (54-79)	0.88
Women	6 (22.2%)	15 (46.9%)	0.049*
Smoking	6 (22.2%)	6 (18.8%)	0.74
Hypertension	22 (81.5%)	26 (81.3%)	0.98
Diabetes	2 (7.4%)	5 (15.6%)	0.44
AF	6 (22.2%)	9 (28.1%)	0.6
Previous stroke	7 (25.9%)	4 (12.5%)	0.32
HbA1c (%)	5.6 (5.3-6.2)	5.6 (5.3-5.8)	0.82
LDL-Cholesterol (mg/dl)	108 (83-121)	113.5 (84.8-147)	0.36
Headache	6 (24%)	14 (45.2%)	0.1
No focal neurological manifestations**	1 (3.7%)	11 (34.4%)	0.004
NIHSS on admission	2 (1-5)	2 (0-4)	0.16
Good outcome on discharge	22 (81.5%)	25 (78.1%)	0.75
Onset of symptoms till presentation in hours§	4 (2-12)	7.5 (4-46)	0.052
Wake-up stroke or found with stroke	6 (18.8%)	5 (15.2%)	0.7
Onset to MRI in hours	49 (23-84)	40 (19-75)	0.39
Bilateral infarction	5 (18.5%)	7 (21.9%)	0.75
Infarction location			
Cerebellum or brain stem	14 (51.9%)	30 (93.8%)	<0.001*
Cerebellum or dorsal brain stem	11 (40.7%)	29 (90.6%)	<0.001
Cerebellum	9 (33.3%)	26 (81.3%)	<0.001*

Cerebellar tonsil	2 (7.4%)	15 (46.9%)	0.001*
Cerebellar nodulus	1 (3.7%)	7 (21.9%)	0.06
Dorsal brain stem	3 (11.1%)	7 (21.9%)	0.32
Total infarction volume in cm3	0.42 (0.14-8.4)	5.6 (0.98-25.5)	0.008*
Total infarction volume of >0.48 cm3	12 (44.4%)	27 (84.4%)	0.002*
Volume of infarction located in the cerebellum and/or brainstem	0.24 (0.11-0.38) (n=14)	5.6 (0.77-24.01) (n=30)	<0.001*
Volume of infarction located in the cerebellum	0.26 (0.12-4.92) (n=9)	9.09 (2.4-25.26) (n=26)	0.001*
Volume of infarction located in the brainstem	0.11 (0.05-0.27) (n=7)	0.10 (0.05-0.5) (n=9)	0.92
Intravenous thrombolysis	10 (37%)	5 (15.6%)	0.06

Results are expressed as absolute values (percentages) or median (interquartile range)

*Statistically significant, **Focal neurological manifestations was defined as the presence of neurological manifestations on presentation allowing the localization to one cerebral hemisphere, §In patients with wake-up stroke or those found with stroke, the time of symptom onset was accepted as the time, when the patient was found with stroke

Table 2: Factors related to the development of vertigo in the binary logistic regression models

Characteristic	Univariate regression analysis			Multivariate regression analysis		
	OR	95% CI	P	OR	95% CI	P
Age in years	0.99	96-1.03	0.72	0.96	0.9-1.02	0.17
Women	3.09	0.99-9.68	0.053	3.8	0.79-18.47	0.1
Smoking	0.81	0.23-2.87	0.74			
Hypertension	0.99	0.26-3.67	0.98			
Diabetes	2.32	0.41-13.03	0.34			
AF	1.37	0.42-4.5	0.61			
Previous stroke	0.41	0.11-1.58	0.2			
HbA1c (%)	1	0.55-1.8	1			
LDL-cholesterol (mg/dl)	1.01	0.99-1.02	0.51			
White blood cells*1000/µl	1.08	0.9-1.29	0.41			
C-Reactive-Protein	0.71	0.44-1.16	0.17			
Erythrocyte sedimentation rate in the first hour (mm)	0.99	0.96-1.02	0.62			
Total infarction volume of >0.48 cm3	6.75	1.99-22.85	0.002*	4.4	1.05-18.58	0.043*
Infarction affecting the cerebellum or dorsal brain stem	14.06	3.42-57.88	<0.001*	16.97	3.1-92.95	0.001*

*Statistically significant

**The periventricular and the deep white matter lesions white matter lesions were assessed in every side separately using Fazekas scale and the mean value was used in the statistical analysis

Figures

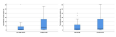

Figure 1

A. Total infarction volume among vertigo (+) patients versus vertigo (-) patients (p=0.008).

B. Total infarction volume among male and female patients (p=0.11).

Figure 2

Diffusion weighted magnetic resonance imaging showing examples of patients with vertebrobasilar stroke having vertigo. A. and B. affection of the nodulus (long thin arrow), C. affection of the dorsal pons, probably in the nucleus prepositus hypoglossi (short thick arrow), D. through F affection of the cerebellar tonsil (double long thin arrows). Note the large infarction size in comparison to Figure 3.

Figure 3

Diffusion weighted magnetic resonance imaging showing examples of patients with vertebrobasilar stroke without vertigo. A. Minute infarction in the vermis (long thin arrow), B. and C. Minute infarction in the cerebellar hemisphere (long thin arrow), D. Large infarction affecting the cerebellar hemisphere and tonsil (short thick arrow), E. Multiple infarctions affecting the ventral pons (long thin yellow arrow) and the cerebellar hemisphere (long thin arrow), F. Minute infarction affecting the dorsal pons (long thin arrow). Note the small size of the infarctions in comparison to Figure 2.