Brain structure and stroke risk score in subjects without a history of atrial fibrillation

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ABSTRACT

CHA2DS2-VASc score system aids in clinical decision-making in subjects with atrial fibrillation (AF). Little is known on the association between CHA2DS2-VASc scores and brain structure in patients without cardiac arrhythmia. Detailed brain architecture analysis was performed. Assessment of bivariate correlation between the volume of segmented brain structures and Z-scores of CHA2DS2-VASc showed that higher risk scores correlated negatively and significantly with various brain framework. Our study confirms that a cluster of risk factors incorporated in a well-established risk score correlated with brain tissue volume independently of the presence of an arrhythmia.

ARTICLE HISTORY

Received 11 August 2021
Revised 25 April 2022
Accepted 1 May 2022

KEYWORDS
Risk score; brain structure; brain segmentation; atrial fibrillation

Introduction

It is well known that atrial fibrillation/flutter (AF) is associated with an increased risk of stroke and cognitive impairment. Moreover, AF is associated with decreased brain volume measures. The primary and most devastating consequence of atrial fibrillation/flutter is stroke. CHA2DS2-VASc score was developed to predict the risk of thromboembolism in patients presenting with atrial fibrillation/flutter. This risk calculator serves primarily for clinical decision-making to start anticoagulation in subjects with AF [1]. However, a new application was also researched, e.g. Berkovitch et al. [2] demonstrated that CHA2DS2-VASc could be used to predict new-onset AF among asymptomatic middle-aged adults. Mayasi et al. [3] demonstrated after adjustment for the CHA2DS2-VASc score that the link between AF and brain injury extends beyond thromboembolic complications. Song et al. [4] found that the frequency of cerebral microbleeds increases with CHA2DS2-VASc scores. Thus this standard risk assessment tool is increasingly used for purposes other than clinical aids decision.

We investigate whether exists a mechanistic correlation between risk score obtained with the use of CHA2DS2-VASc, and brain structure estimated by magnetic resonance imaging (MRI) in patients without documented atrial fibrillation/flutter.

Material and methods

The study population consisted of 191 patients subjected to routine brain MRI performed during a neurological assessment for transient ischemic attacks (TIA) or a history of stroke. The exclusion criteria from the analysis included new or previous atrial fibrillation/flutter and implanted electronic devices. Exclusion of AF was based on patients history and available (for prior 5 yrs) electronic health records, as well as current hospital data.

CHA2DS2-VASc score system included: congestive heart failure/left ventricle dysfunction (score 1), hypertension (score 1), age (>65 years score 1, >75 years score 2), diabetes mellitus (score 1), stroke/TIA (score 2), vascular disease (prior myocardial infarction, peripheral artery disease, aortic plaque) – score 1, sex (female sex score 1).

The University Ethics Committee approved the study protocol. Inform written consent was obtained from patients during hospitalization. We did not collect separate consent for the analysis of the existing database.

Brain magnetic resonance imaging and segmentation

The brain imaging was performed by 1.5T MRI scanner (Avanto Siemens Medical System, Germany) with a 12-channel head RF coil. Besides routine brain protocol containing axial, sagittal T1-weighted, T2-weighted, FLAIR and DWI sequences, we also obtained three-dimensional T1-weighted image (MPRAGE- Magnetisation Prepared Rapid Acquisition Gradient Echo; TR/TE/IR: 2400 ms/3.61ms/1000 ms; section thickness: 1.2 mm) to assess volumes of brain regions.

Detailed brain structure segmentation was performed with a FreeSurfer software (Laboratory for Computational
Neuroimaging, Athinoula A. Martinos Center for Biomedical Imaging).

**Statistical analysis**

All analyses were performed with SPSS (version 26.0, IBM Corp, USA). Continuous data are reported as a mean ± SD. Baseline characteristics are reported as standard descriptive statistics. Differences between groups were estimated using Student’s t-test. Z-score for CHA2DS2-VASc was calculated. The interrelationships between metrics were assessed using Spearman’s correlation. All tests were two-sided, and \( p < .05 \) was considered significant. A regression analysis of brain segments volume was performed, to evaluate which component of CHA2DS2-VASc contributes significantly to brain segments volume. To account for the differences in body mass, brain volumes were adjusted to body mass index (BMI).

**Results**

One hundred ninety-one subjects were evaluated (75 females, 116 males), mean age 70 ± 10 years, details are presented in Table 1.

Analysis of bivariate correlation between the volume of segmented brain structures and Z-scores of CHA2DS2-VASc showed that higher risk score correlated negatively and significantly with amygdala volume \((r = -0.21, p = .003)\), putamen \((r = -0.2, p = .03)\), thalamus \((r = -0.36, p = .001)\), gray matter \((r = -0.18, p = .01)\), white matter \((r = -0.34, p = .001)\) but not with hippocampus \((r = -0.14, p = .06)\) or pallidum \((r = 0.19, p = .8)\); example of strongest correlation is presented in Figure 1 (Part A and Part B).

There was no significant difference between age and brain segments volume in subgroups of subjects who suffered from TIA or stroke, except for pallidum. Mean age of TIA patients 70.2 ± 10.9 years vs. 69.8 ± 9.9 subjects who suffered stroke, \( p = .9 \). Caudate (6.7 ± 1.5 cm³ vs. 6.8 ± 1.4 cm³, \( p = .6 \)), putamen (7.3 ± 1.2 cm³ vs. 7.6 ± 1.1 cm³, \( p = .3 \)), pallidum (3.9 ± 0.6 cm³ vs. 4.2 ± 0.7 cm³, \( p = .008 \)), hippocampus (7.7 ± 1.2 cm³ vs. 9.1 ± 0.9 cm³, \( p = .2 \)), amygdala (2.6 ± 0.5 cm³ vs. 2.7 ± 0.4 cm³, \( p = .1 \)), gray matter (458.9 ± 56 cm³ vs. 471.3 ± 41 cm³, \( p = .3 \)), white matter (703.1 ± 122.4 cm³ vs. 688.2 ± 102.4 cm³, \( p = .5 \)).

In regression analysis, amygdala/BMI volume was associated significantly and negatively with female sex and diabetes, putamen/BMI with female sex and diabetes (DM), thalamus/BMI with hypertension, DM and older age, gray matter volume (GMV)/BMI with DM and female sex while white matter volume (WMV)/BMI with DM, hypertension and female sex (data not shown).

**Discussion**

We demonstrated that an increased risk score estimated by CHA2DS2-VASc in patients without documented atrial fibrillation/flutter is significantly associated with the atrophy of various brain structures.

It was established that various pathological processes are associated with a harmful impact on brain volume. Gray matter areas related to cognitive function showed morphological changes in subjects with heart failure, increased BMI, hypertension, or diabetes in comparison with healthy controls [5-7].

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**Table 1.** Clinical characteristics of the study participants.

| Characteristic                  | Total population |
|--------------------------------|------------------|
| Number of subjects             | 191              |
| Females/males                  | 75/116           |
| Age, years                     | 69.9 ± 9.9       |
| BMI, kg/m²                     | 27.8 ± 5.1       |
| BPsystolic, mmHg               | 145.9 ± 21.8     |
| BPdiastolic, mmHg              | 81.2 ± 12.1      |
| CHA2DS2-VASc                   | 4.3 ± 1.5        |
| TIA                            | 162              |
| Hypertension                   | 140              |
| Diabetes                       | 58               |
| Myocardial infarction          | 16               |
| Vascular disease               | 42               |
| Cortical gray matter (cm³)     | 460.8 ± 54.5     |
| White matter (cm³)             | 700.8 ± 119.4    |
| Hippocampus (cm³)              | 7.8 ± 1.2        |
| Amygdala (cm³)                 | 2.6 ± 0.5        |
| Caudate (cm³)                  | 6.7 ± 1.5        |
| Putamen (cm³)                  | 7.4 ± 1.2        |
| Thalamus (cm³)                 | 14.6 ± 2.1       |
| Pallidum (cm³)                 | 3.9 ± 0.7        |

BMI: Body mass index; BP: blood pressure; TIA: transient ischemic attacks.

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**Figure 1.** Correlation between Z-scores of CHA2DS2-VASc and thalamus volume (Part A) and (Part B) white matter volume (WMV).
CHA$_2$DS$_2$-VASc score represents a frequently use and well-established lump measure of risk factors associated with stroke in subjects with atrial fibrillation/flutter. We demonstrated that gray matter and white matter volume were negatively and significantly correlated with a higher risk score estimated by CHA$_2$DS$_2$-VASc. Moreover, a higher value of CHA$_2$DS$_2$-VASc risk metric was associated with a decreased volume of the amygdala, putamen, and thalamus, but not hippocampus or pallidum. Furthermore, out of all the elements included in CHA$_2$DS$_2$-VASC scoring, diabetes mellitus was the most often contributing factor significantly associated with lower segmental brain volume. These selected brain structures play an essential role in memory, cognition, thought, behavior, and perception. We also noticed that there was no difference in segmented brain volume between subjects with TIA and those who suffered a stroke in the past. Thus, a brain volume loss was not a consequence of severe central nervous system insults.

It was demonstrated that asymptomatic subjects experience continuing brain volume loss, which appears to accelerate with age [8]. Kern et al. [9] showed that controlling blood pressure might limit the effects of small-vessel disease and aging on cerebral gray matter atrophy. White matter hyperintensities (WMH) are associated with stroke and cognitive decline [10]. Moreover, white matter injury is associated not only with cardiovascular risk factors but also with brain atrophy [11]. Several mechanisms may be responsible for the adverse effects of vascular risk factors on brain volume. In the case of, e.g., diabetes, impaired insulin signaling leads to neuroinflammation, oxidative injury, and oxygen stress resulting in progressive neurodegeneration [12]. Since brain atrophy is a risk factor for cognitive decline, it is tempting to speculate that easily obtained brain atrophy predictor may potentially serve as an indicator that selects subjects for preventing measures that may delay the onset of cognitive sequelae.

In summary, our study seems to confirm that a cluster of risk factors incorporated in a well-established risk score correlated with brain tissue volume independently of the presence of a documented arrhythmia.

**Study limitation**

Our study has several limitations. First, results are obtained from the analysis of the existing database. Moreover, all subjects within the study suffered from TIA/stroke, which may influence obtained results. Second, we did not include age-matched healthy controls. Third, the observed correlation does not imply causal relationships. Fourth, it is well established that implantable electrocardiographic monitoring for 12 months, compared with prolonged external monitoring for 30 days, resulted in a more significant proportion of patients with AF detected over 12 months (15.3% vs. 4.7%) [13]. Therefore, we cannot rule out paroxysmal FA in some of our patients.

**Author contributions**

KK, MW conceived the idea for the study, analysis, and manuscript preparation. AKZ contributed to the design of the research. AKZ helped in data collection. MW, KK, AKZ, LG analyzed the data. KK coordinated the project. All authors edited and approved the final version of the manuscript.

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

**Funding**

Unrestricted internal research grant from University of Medical Science Poznan Poland.

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