JVIN Journal of Vascular and Interventional Neurology
OFFICIAL JOURNAL OF THE ZEENAT QURESHI STROKE INSTITUTE

Neuroanatomical correlates of atrial fibrillation: a longitudinal MRI study

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Abstract

Background and purpose—To determine baseline volume and rate of volume change of whole brain, hippocampus, and entorhinal cortex in patients with atrial fibrillation.

Methods—We analyzed clinical and neuroimaging data collected as part of Alzheimer's Disease Neuroimaging Initiative in the United States and Canada. Patients with atrial fibrillation were identified based on baseline clinical/cognitive assessments, and age and gender-matched controls without atrial fibrillations were selected (1:1 ratio). All participants underwent 1.5 T structural magnetic resonance imaging (MRI) at specified intervals (6 or 12 months) for 2–3 years.

Results—A total of 33 persons with atrial fibrillation were included. There was no difference in whole brain and ventricular volumes at baseline MRI between cases and controls. There was significantly lower entorhinal cortex volume on right (p = 0.01) and left (p = 0.01) sides in patients with atrial fibrillation. There was significantly lower volume for middle temporal lobes on right (p = 0.04) and left (p = 0.001) sides. The rate of progression of atrophy in entorhinal cortex and middle temporal lobes was not different between patients with atrial fibrillation and controls.

Conclusions—The association of atrial fibrillation with volume loss in entorhinal cortex and middle temporal lobes may provide new insights into pathophysiology of atrial fibrillation.

Keywords

Atrial fibrillation; entorhinal cortex; volume loss; magnetic resonance imaging (MRI); temporal lobe

Introduction

Patients with atrial fibrillation have an increased risk of cognitive decline in the absence of ischemic stroke [1,2]. Stroke-free individuals with atrial fibrillation had worse performance in learning and memory tasks compared with persons without atrial fibrillation in one study [3]. There is some evidence that cognitive decline in persons with atrial fibrillation is related to hippocampal volume loss [3]. Furthermore, the temporal lobe significantly effects modulation of cardiac rate and excitability [4–6]. On the basis of the association of atrial fibrillation with cognitive decline and influence of brain on modulation of cardiac rate and excitability, we tested the hypothesis that structural changes in the brain are associated with atrial fibrillation.

Methods

We analyzed clinical and neuroimaging data collected as part of Alzheimer's Disease Neuroimaging Initiative (ADNI). ADNI is an ongoing, longitudinal, multicenter study designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of Alzheimer's disease [7]. The ADNI study began in 2004 and included 400 subjects diagnosed with mild cognitive impairment (MCI), 200 subjects with early AD and 200 elderly control subjects from 200 normal controls recruited at approximately 50 sites in the United States and Canada.

Data used in the preparation of this article were obtained from the ADNI database (www.loni.ucla.edu\ADNI).

Published December, 2014.

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The goal of ADNI was to recruit 800 adults, aged 55–90, to participate in the research—approximately 200 normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with early Alzheimer's disease to be followed for 2 years (www.adni-info.org). The presence of cardiovascular risk factors including hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, prior stroke, or myocardial infarction is recorded for each participant. Any history of depression or cancer is recorded as well. The mini mental status evaluation (MMSE) scores at baseline and followup visits are determined as part of ADNI.

All ADNI participants with structural magnetic resonance imaging (MRI) images whose MRI scans were analyzed and results available on the ADNI website as of February 2007 (the latest scan was from 19 December 2006) were included. The data sets included standard T1-weighted MR images acquired sagittally using volumetric 3-D MPRAGE with 1.25 × 1.25 mm in-plane spatial resolution and 1.2–mm-thick sagittal slices (8° flip angle). Most of the images were obtained using 1.5 T scanners, while a few were obtained using 3 T scanners. Detailed information about MR acquisition and analyses procedures is available in previous publications [8,9]. All participants underwent 1.5 T structural MRI at specified intervals (6 or 12 months) for 2–3 years.

Briefly, images were first preprocessed by alignment to the AC–PC plane and removal of extracranial material. Brain tissue was segmented into grey matter, white matter, and cerebrospinal fluid, using a brain tissue segmentation. After high-dimensional image warping to a standardized brain atlas (template), regional volumetric maps, termed RAVENS maps were used to quantify the regional distribution of gray matter, white matter, and cerebrospinal fluid. The RAVENS approach [10,11] uses highly conforming high-dimensional image warping algorithm and tissue-preserving transformations that captures finer structural details and preserves the amount of grey matter, white matter, and cerebrospinal fluid tissue present. A high-dimensional pattern classification approach identifies a minimal set of regions as follows: hippocampus, inferior lateral ventricle, middle temporal lobe, inferior temporal lobe, fusiform lobe, and entorhinal lobe. Total brain, intracranial, and ventricular volumes are quantified as well.

Patients with atrial fibrillation were identified based on baseline clinical assessments and age and gender-matched controls without atrial fibrillations were selected (1:1 ratio). If an appropriate age matched control was not identified, a control aged 1 year less or more was selected.

Statistical analysis

Univariate analyses were performed comparing continuous variables with ANOVA and categorical variables using chi-square test between patients with atrial fibrillation and age- and sex-matched controls. The correlation coefficient was determined between the MMSE score and volume of selected regions of brain in patients with atrial fibrillation. The correlation coefficient was determined between the rate of MMSE change and change in volume of selected regions of brain in patients with atrial fibrillation.

Results

A total of 33 persons with atrial fibrillation were included [mean (±SD) 78 ± 6, 22 were men]. There were no patients in the atrial fibrillation group with stroke and four controls who had a previous history of stroke. The proportion of patients with hypertension (63.6% versus 36.3%, 0.02) and hyperlipidemia (63.6% versus 39.3%, $p = 0.04$, see Table 1) were higher in persons with atrial fibrillation compared with controls. The proportion of patients with cancer was higher among persons with atrial fibrillation (54.5% versus 36.3%, $p = 0.13$). The mean MMSE score (±SE) was lower among persons with atrial fibrillation compared with age and gender-matched controls (28±0.3 versus 30±0.1, $p = 0.002$).

There was no difference in whole brain, intracranial, and ventricular volumes at baseline MRI between cases and controls. There was no difference between right and left hippocampus volumes between persons with atrial fibrillation and controls. The volumes of inferior temporal cortex and fusiform cortex on both sides were similar between person with atrial fibrillation and controls. There was significantly lower entorhinal cortex volume on right ($p = 0.01$) and left ($p = 0.01$) sides in patients with atrial fibrillation. There was significantly lower volume for middle temporal lobes on right ($p = 0.04$) and left ($p = 0.001$) sides. Among patients with atrial fibrillation, there was a direct correlation between MMSE scores and left entorhinal cortex ($r^2 = 0.5$, $p = 0.001$), and right entorhinal cortex ($r^2 = 0.3$, $p = 0.05$) but not with left middle temporal lobe ($r^2 = 0.1$, $p = 0.5$), and right middle temporal lobe ($r^2 = 0.2$, $p = 0.2$).

There was a trend in higher rate of MMSE score decrease per year in persons with atrial fibrillation than that of the control group with a p value of 0.09. The average rate of MMSE score annual decrease (mean ±

Table 1. Demographic and clinical characteristics of, and volumes of various brain regions in patients with atrial fibrillation and age- and sex-matched controls.

	Cases with atrial fibrillation	Controls without atrial fibrillation	*p*-Value
Overall numbers (%)	33	33	
Age (mean ± SD)	78 ± 6	79 ± 6	0.8
Gender			
Men	22	27	
Women	11	6	0.15
Race			
White	33	33	0.31
Comorbid conditions			
Depression	8 (24.2)	4 (12.1)	0.2
Hypertension	21 (63.6)	12 (36.3)	0.02
Diabetes mellitus	1 (3.0)	3 (9.0)	0.3
Renal failure	2 (6.0)	0 (0)	0.15
Stroke	0 (0)	4 (12.1)	0.03
Hyperlipidemia	21 (63.6)	13 (39.3)	0.04
Myocardial infarction	3 (10.0)	0 (0)	0.06
Cancer	18 (54.5)	12 (36.3)	0.13
Brain volumes (mean ± SE)			
Total brain (baseline)	977245±17220	1025784±15314	0.79
Total brain (6 months)	975985±15677	1312560±289055	0.001
Total brain (12 months)	971778±17975	996120±35014	0.001
Intracranial volume (baseline)	1455763±30272	1522678±21730	0.16
Intracranial volume (6 months)	1472983±24062	1517552±21138	0.89
Intracranial volume (12 months)	1472983±24062	1526397±21084	0.76
Ventricles (baseline)	44198.3±4685	43627.2±3761	0.42
Ventricles (6 months)	45597.4±4816	45580.5±3946	0.32
Ventricles (12 months)	47000.1±5595	47514.3±4077	0.21
Left hippocampus (baseline)	3202.2±89	3579.6±96	0.44
Left hippocampus (6 months)	3199.8±81	3555.7±94	0.35
Left hippocampus (12 months)	3167±91	3545.4±99	0.43
Right hippocampus (baseline)	3299.3±87	3769.9±100	0.26
Right hippocampus (6 months)	3316.9±81	3736.9±99	0.24
Right hippocampus (12 months)	3281.8±97	3733.7±101	0.56
Left inferior lateral ventricle (baseline)	1386.9±144	1512.8±172	0.18
Left inferior lateral ventricle (6 months)	1531.4±160	1606±188	0.33
Left inferior lateral ventricle (12 months)	1538.1±183	1659.8±206	0.33
Right inferior lateral ventricle (baseline)	1535.1±155	1514.3±183	0.23
Right inferior lateral ventricle (6 months)	1663.7±172	1591±200	0.37
Right inferior lateral ventricle (12 months)	1755.4±210	1698±212	0.67
Left middle temporal (baseline)	2.419±64	2.561±0.03	0.001
Left middle temporal (6 months)	2.4453±0.03	2.5498±0.03	0.97
Left middle temporal (12 months)	2.441±0.03	2.5332±0.03	0.96
Right middle temporal (baseline)	2.4886±0.04	2.593±0.03	0.04
Right middle temporal (6 months)	2.496±0.04	2.5894±0.03	0.27
Right middle temporal (12 months)	2.482±0.04	2.563±0.03	0.26
Left inferior temporal (baseline)	2.5181±0.03	2.6213±0.03	0.78
Left inferior temporal (6 months)	2.5042±0.03	2.6139±0.03	0.86
Left inferior temporal (12 months)	2.4906±0.03	2.5985±0.03	0.57
Right inferior temporal (baseline)	2.4859±0.04	2.5675±0.03	0.88
Right inferior temporal (6 month)	2.474±0.04	2.5614±0.03	0.68
Right inferior temporal (12 months)	2.4537±0.04	2.5498±0.04	0.88
Left fusiform (Baseline)	2.2947±0.03	2.3463±0.03	0.97
Left fusiform (6 month)	2.2838±0.03	2.3632±0.03	0.58
Left fusiform (12 month)	2.289±0.03	2.3311±0.03	0.44
Right fusiform (baseline)	2.2774±0.03	2.3587±0.03	0.75
Right fusiform (6 months)	2.2651±0.03	2.3488±0.03	0.79
Right fusiform (12 months)	2.2515±0.03	2.3368±0.03	0.37
Left entorhinal (baseline)	2.9021±0.09	3.1611±0.05	0.01
Left entorhinal (6 months)	2.8962±0.09	3.1749±0.06	0.02
Left entorhinal (12 months)	2.8907±0.1	3.1491±0.06	0.001
Right entorhinal (baseline)	3.0807±0.1	3.358±0.06	0.01
Right entorhinal (6 months)	3.1155±0.1	3.3745±0.06	0.01
Right entorhinal (12 months)	3.1076±0.1	3.3331±0.06	0.004

Abbreviation:SD: standard deviation, SE: standard error.

SE) was −0.54 ± 0.2 for the atrial fibrillation group and −0.42 ± 0.3 for the control group. The rate of progression of atrophy in entorhinal cortex and middle temporal lobes was not different between patients with atrial fibrillation and controls. Among persons with atrial fibrillation, the correlation coefficient between the relationship of the rate of MMSE change and change in volume of left entorhinal cortex (r^2 = 0.2), right entorhinal cortex (r^2 = 0.3), left middle temporal lobe (r^2 = 0.2), and right middle temporal lobe (r^2 = 0.2) was not significant.

Discussion

We observed evidence of volume loss of middle temporal lobes and entorhinal cortex in patients with atrial fibrillation. Temporal lobe atrophy has particular significance in patients with atrial fibrillation due to increased risk of cognitive decline in the absence of ischemic stroke [1,2]. Stroke-free individuals [3] with atrial fibrillation had worse performance in learning and memory tasks compared with persons without atrial fibrillation from the same community. The hippocampal volume was also reduced in patients with atrial fibrillation. There was no significant association of atrial fibrillation with total brain volume or white matter volume. Entorhinal cortex is integrated closely with hippocampus within the temporal lobe through multiple fiber projections [12,13]. The entorhinal cortex provides major input pathways to the hippocampus and may process the details of various elements of memory [14]. Atrophy of entorhinal cortex has been seen in association with temporal lobe atrophy in elderly persons [15]. Neurofibrillary triangles can also be seen in entorhinal cortex in experimental models of Alzheimer's disease [16].

Relative cerebral hypoperfusion induced by cardiac beat-to-beat variability in patients with atrial fibrillation can lead to silent ischemia of ischemia vulnerable areas such as the medial temporal lobe [17]. In one study [17], the median cerebral blood flow increased from 35.8 ml/min/100 g to 46.7 ml/min/100 g after cardioversion in patients with atrial fibrillation. The reduction in cerebral blood flow may be secondary to lower cardiac output associated with atrial fibrillation [18]. Atrial fibrillation is associated with a greater rate of cognitive decline in patients with Alzheimer disease [19]. A faster rate of accumulation of β-amyloid and tau proteins, and amyloid fibrils within the temporal lobes may lead to atrophy by cytotoxic effects [20]. Amyloid fibrils and amyloid deposits are also present in the atria of patients with atrial fibrillation suggesting a related pathogenesis [21]. We had excluded patients with Alzheimer's disease but hippocampal atrophy can occur prior to clinical diagnosis [22]. Concurrent hyperlipidemia maybe associated with temporal lobe atrophy in patients with atrial fibrillation. Treatment with atorvastatin and ezetimibe for 1 year prevented temporal lobe atrophy in patients with atrial fibrillation in a double-blinded randomized trial [23]. Such treatment was associated with reduction in serum inflammatory markers and improvement in neuropsychological performance.

Certain pathways that are common between atrial fibrillation and cognitive decline may be involved. MicroRNA-328 contributes to adverse electrical remodeling in atrial fibrillation [24]. MicroRNA-38 also regulates expression of mouse beta-amyloid precursor protein-converting enzyme 1 [25]. Inward rectifier K^+ channels are involved in electrical current modulation in entorhinal cortex [26] and atria in atrial fibrillation [27] Abnormalities in genes that code inward rectifier K+ channels have been associated with atrial fibrillation [28] and cognitive impairment [29]. Altered expression of genes predisposing to the development of fibrosis (e.g., upregulation of transforming growth factor β1 has been identified in atrial fibrillation [30] and Alzheimer's disease [31]).

The possibility that volume loss in the temporal lobes may contribute to genesis or propagation of atrial fibrillation needs to considered. Tachycardia and abnormal QTc prolongation are associated with increase in hippocampal activity during predominantly left hippocampal seizures [4]. Transcranial stimulation of the left temporal lobe enhances the parasympathetic and decreases the sympathetic modulation of heart rate [5] and excessive activity during seizures can result in asystole [6]. The regulation of heart rate variability is altered with impairment in baroreflex function in temporal lobe epilepsy [32,33]. After surgical resection of temporal lobe in patients with intractable temporal lobe epilepsy, sympathovagal balance, and heart rate variability is altered with sympathetic activity exceeding parasympathetic activity after the first month of surgery [34].

The association of atrial fibrillation with volume loss in entorhinal cortex and middle temporal lobes may provide new insights into pathophysiology of atrial fibrillation and associated cognitive deficits.

Acknowledgments

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu\ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. Complete list of ADNI investigators is available at http://www.loni.ucla.edu/ADNI/Data/ADNI_Manuscript_Citations.doc.

Dr. Qureshi has received funding from the National Institutes of Health RO1-NS44976-01A2 (medication provided by ESP Parma), American Heart Association Established Investigator Award 0840053N, National Institute of Health U01-NS062091-01A2, and the Minnesota Medical Foundation, Minneapolis, MN.

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