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Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Medicine

journal homepage: http://ees.elsevier.com/apjtm

Original research http://dx.doi.org/10.1016/j.apjtm.2017.08.019

Relationship between abnormal vagus nerve tension and basal ganglia cerebral infarction induced paroxysmal atrial fibrillation

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ARTICLE INFO

Article history:
Received 4 Jul 2017
Received in revised form 25 Aug 2017
Accepted 30 Aug 2017
Available online 14 Sep 2017

Keywords:
Basal ganglia
Cerebral infarction
Abnormal vagus nerve tension
Paroxysmal atrial fibrillation

ABSTRACT

Objective: To investigate the relationship between basal ganglia cerebral infarction and paroxysmal atrial fibrillation (PAF) caused by abnormal vagus nerve tension.
Methods: A total of 1 483 cases of elder patients with cerebral infarction who received head CT or MRI examination during the period were enrolled, including 830 male and 613 female, with the average age as 78 years. These cases were divided into basal infarction ganglia group (n = 1 045) and non-basal ganglia infarction group (n = 438) according to the anatomic site of cerebral infarction. The differences of the incidence of PAF, left atrial diameter and heart rate variability were compared between the two groups.
Results: In basal ganglia infarction group, the incidence rate of PAF was significantly higher than that of non-basal ganglia infarction group ($P < 0.05$). The incidence trend of cerebral infarction in basal ganglia was age-related, in the >79 years basal ganglia cerebral infarction group, the incidence of PAF was significantly higher than that of non-basal ganglia infarction group ($P < 0.05$). There was no significant difference in the left atrial diameter between the basal ganglia infarction group and non-basal ganglia infarction group. Basal ganglia cerebral infarction patients with high PAF had higher heart rate variability than non-basal ganglia infarction group.
Conclusion: Elderly patients with basal ganglia infarction have high incidence of PAF. Sympathetic nerve damage in cerebral basal ganglia, increased vagal tension and cardiac vagal tension are the direct causes of PAF. The results indicates that the increased central vagal nerve tension mediated PAF probably is an indication of supplying sympathetic neurotransmitter or cardiac vagal denervation treatment.

1. Introduction

Atrial fibrillation (AF) is one of the most common arrhythmia, which could cause clinical thrombosis, heart failure, higher hospitalization rates and high mortality. With the development of drugs, intervention and implantation devices, AF treatment efficacy has been greatly improved. The research of autonomic nerve imbalance has been a hot topic in studying the mechanisms of AF. Basic and clinical studies have shown that vagus nerve tension is highly related with paroxysmal atrial fibrillation (PAF). Although there are many predictions about the causes of vagus hypertension, no exact mechanisms have been clearly described. The mechanisms, clinical diagnosis and treatment of cerebral embolism in atrial fibrillation have made significant progressed [1]. In recent years, our clinical study found that vascular Parkinson's disease (VP) with basal ganglia cerebral infarction in elderly patients have severe PAF or sinus bradycardia without levodopa treatment, and this syndrome with be effectively controlled after drug treatment recovery. This phenomenon remind us that cerebral infarction caused by central sympathetic nerve injury is the major reason of the higher central vagus nerve tension triggered PAF. Understanding the causes of PAF and the target of the central sympathetic neurotransmitter might provide new treatment

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Peer review under responsibility of Hainan Medical University.
Foundation project: This work was funded by Shanghai Health and Family Planning Commission Youth Found to Wenbo Cheng (20144Y0116).

method for PAF patients caused by the increased central vaginal nerve tension.

2. Materials and methods

2.1. Patients

In this study, 1 483 patients with cerebral infarction who received head CT or MRI diagnosis in the hospital from January 2013 to December 2014 were selected, which included 838 males and 645 females, 38–92 years, with mean age of 78 years. A total of 1 045 (70.4%) had basal ganglia cerebral infarction, and 438 (29.6%) had non-basal ganglia cerebral infarction. The detail of cerebral infarction patients were as described in Table 1.

Patients were divided into two groups, basal ganglia cerebral infarction group and non-basal ganglia cerebral infarction group, by comparing the incidence of PAF, left atrial diameter and heart rate variability, the correlation between basal ganglia cerebral infarction and abnormal vagus nerve tension caused PAF were explored.

Patients with the following diseases were excluded from the study: (1) Persistent atrial fibrillation; (2) Cardiovascular disease: heart valve disease, congenital heart disease, congestive heart failure; (3) Liver and kidney disease: active liver disease, liver and kidney dysfunction; (4) Malignant tumor; (5) Functional failure; (6) History of dementia and mental illness; (7) Inflammation and rheumatism; (8) Acute cerebral infarction.

2.2. Methods

The general clinical data in these cases were collected according to the diagnostic criteria of patients with PAF, the number of patients with PAF was counted, and the dynamic electrocardiogram and echocardiography (ECG) results were collected from patients with PAF and basal ganglia.

PAF patients' criteria were as follows: patient's clinical symptoms and signs were consistent with the definition of PAF by ECG or 24-h ambulatory ECG confirmation. Atrial fibrillation usually will be self-terminated within 48 h, and the longest termination time was less than 7 d.

2.3. Heart rate variability analysis

Patient data were collected and analyzed by the United States PI company three-channel dynamic ECG analysis system. Man-machine dialogue method was used to remove false and non-sinus beat. Following standards were used to analyze the heart rate variability (HRV): the standard deviation of normal RR interval, the average RR interval every 5 min, the root mean square of the difference between the adjacent RRs (RMSSD), the ratio of the number of RR intervals to the proportion of the largest RR interval (HRV triangular index). Frequency was analyzed by fast Fourier transform method, then components and rations of high frequency (HF 0.15–0.40 Hz) and low frequency (LF 0.04–0.15 Hz) were analyzed by fast Fourier transform method.

2.4. Echocardiography

PAF patients' ECG results were collected, the left atrial diameter and ejection fraction were counted.

2.5. Dynamic electrocardiogram examination method

Dynamic electrocardiogram was collected by the United States PI company dynamic ECG system with three channels of 24 h continuous recording. The cardiac active drug was discontinued for 5 d before the examination, and no medication during the examination. The diary and related symptoms were recorded by the patients. Results were recorded and the parameters were analyzed by computer, manually corrected and edited.

2.6. Statistical analysis

Data expressed as mean ± standard deviation were analyzed by the SPSS13.0 software. The t test was used for measured data, and χ^2 test for counted data.

3. Results

3.1. Incidence of PAF in different parts of brain and relevant clinical data

The incidence of PAF in different parts of the brain had no correlation with gender or complications such as coronary heart disease, hypertension, diabetes (Table 2).

The incidence of PAF in the basal ganglia cerebral infarction was 18.37% (192/1 045), and 13.92% (61/438) of that in the

Table 1
Characterization of cerebral infarction patients.

Variable	Basal-gangalia	Non-basal ganglia	Total
Gender			
Men	581	257	838
Women	464	181	645
Complications			
Coronary heart diseases	285	94	479
Hypertension	618	201	924
Diabetes	178	64	319
Age (Years)			
<59	69	49	118
60–69	147	98	245
70–79	428	151	579
>79	401	140	541

Table 2
Information of cerebral infarction patients with PAF.

Groups	Basal-gangalia	Non-basal ganglia	Total
Gender			
Men	101	32	133
Women	91	29	120
Complications			
Coronary heart diseases	129	38	167
Hypertension	141	43	184
Diabetes	39	13	52
Age (Years)			
<59	6	4	10
60–69	19	11	30
70–79	58	21	79
>79	109*	25	134

*$P < 0.05$, compared with non-basal ganglia, difference was statistically significant.

Table 3
Comparison of HRV in different cerebral infarction PAF patients.

Groups	SDNN (ms)		RMSSD (ms)		HRV trigonometry		LF/HF	
	PAF	Non-PAF	PAF	Non-PAF	PAF	Non-PAF	PAF	Non-PAF
Basal-gangalia	268 ± 18[a]	176 ± 22	165 ± 15[a]	135 ± 18	56.9 ± 17.0[a]	42.6 ± 19.0	2.2 ± 1.2[a]	1.25 ± 0.9
Non-basal ganglia	221 ± 20[b]	159 ± 25	128 ± 16[b]	130 ± 22	45.9 ± 16.0[b]	43.9 ± 20.0	1.3 ± 1.1[b]	1.28 ± 1.1

[a] Compared with non-PAF, $P < 0.05$. [b] Compared with basal gangalia, $P < 0.05$.

non-basal ganglia cerebral infarction. There was statistically significant difference between the two groups ($P < 0.05$).

There was no significant difference in the incidence basal ganglia cerebral infarction with PAF and non-basal ganglia cerebral infarction with PAF in the <79 years group (Table 2). The incidence of basal ganglia cerebral infarction with PAF was higher than that of non-basal ganglia cerebral infarction in the >79 years group, there was statistically significant difference ($P < 0.05$). The incidence of PAF was increased with age in basal ganglia cerebral and non-basal ganglia infarction patients.

3.2. ECG information of basal ganglia and non-basal ganglia cerebral infarction caused PAF

In 192 PAF cases cases of basal ganglia cerebral infarction and 61 PAF cases of non-basal ganglia cerebral infarction, there were 81 and 35 cases with useful information respectively. There was no significant difference between the LVEF [(65.0 ± 27.9)% *vs.* (59.0 ± 37.1)%] and the left atrial diameter [(43.3 ± 7.1) mm *vs* (44.1 ± 6.1) mm] of the two groups of PAF patients, which indicated the different incidence of PAF between the two groups was not related to cardiac function and left atrial size.

3.3. HRV of cerebral infarction PAF patients

The indexes of SDNN, RMSSD, HRV trigonometry and LF/HF which represent the vagus nerve tension were significantly higher in PAF patients with basal ganglia cerebral infarction. and were significantly higher than that in 35 PAF patients with non-basal ganglia cerebral infarction ($P < 0.05$) (Table 3). The indexes of SDNN, RMSSD, HRV trigonometry and LF/HF in basal ganglia cerebral infarction patients with PAF was significantly higher than that without PAF ($P < 0.05$). There were no significant differences in the indexes of SDNN, RMSSD, HRV trigonometry and LF/HF between the PAF group and the non-PAF group in non-basal ganglia cerebral infarction patients. The results suggested that the vagus nerve tension was significantly increased in basal ganglia cerebral infarction patients compared with that in non-basal ganglia cerebral infarction patients (Table 3).

4. Discussion

Studies showed that PAF is closely related to cerebral infarction, especially that the asymptomatic PAF has an important role in cerebral infarction. Targeting the etiology and mechanism PAF is an important part for the prevention and treatment of cerebral infarction. Cardiac autonomic nervous system dysfunction is one of the important mechanisms for the development of PAF. Basic and clinical researches have shown that increased vagus nerve tension mediated the occurrence and development of PAF, the main mechanism is the increased vagus nerve tension reconstructed the atrial myoelectric electrophysiology. There are different opinions about how the increased vagus nerve tension causes PAF, targeting vagus nerve tension and its pathogenic mechanism is expected to improve the effectiveness of PAF treatment.

Recently, our clinical study found that interruption of medication will frequently cause PAF and/or severe sinus bradycardia, and the syndromes were controlled after medication recovery during the treatment of elderly VP patients with basal ganglia cerebral infarction, during the treatment of VP. We presumed that the abnormal elderly central cardiac vagus nerve tension caused PAF was triggered by cerebral infarction induced central sympathetic nerve injury, the caused by central sympathetic nerve injury. To obtain further clinical evidence, this study first reviewed the differences in incidence, left ventricular ejection fraction, left atrial diameter and heart rate variability in 1 483 patients with basal ganglia cerebral infarction and non-basal ganglia cerebral infarction. We found that the incidence of PAF in the basal ganglia cerebral infarction group was significantly higher than that in the non-basal ganglia cerebral infarction group, and the incidence of PAF in the basal ganglia cerebral infarction group was not related with LVEF and left atrial diameter, but significantly correlated with increased vagus nerve tension caused heart rate variability index SDNN, RMSSD, HRV trigonometry and LF/HF.

Normal brain regulates the cardiovascular and autonomic nervous function through autonomic nervous system and endocrine mechanisms. Brain-heart interaction in response to physical strenuous exercise, panic, environmental stress and mood changes, *etc*., can coordinately regulate the cardiac activity and vasomotor function. Studies have shown that stroke has a significant impact on the heart; different parts of the cerebral infarction have different effects on the heart. The left side cerebral hemisphere infarction usually causes ECG repolarization, myocardial enzymes and myocardial cell focal solubility changes. Meanwhile, the right side of the cerebral hemisphere infarction frequently causes atrial arrhythmia, with AF up to 31% [2–4]. Our study first found that the basal ganglia is the most frequent part for the elderly patients with cerebral infarction, < 60 years group was 6.6%, 60–69 years group was 14.1%, 70–79 age group was 40.9%, > 79 years group was 38.4%. We further described that, the incidence of PAF in the basal ganglia was high, 18.37% in the basal ganglia infarct group, 13.92% in the non-basal ganglia infarct group, in the > 79 years group, the incidence of PAF was 56.8% in the basal ganglia and 40.9% in the non-basal ganglia cerebral infarction group. The increased incidence of PAF in basal ganglia cerebral infarction group was not correlated with left ventricular ejection fraction and left atrial diameter.

The incidence of PAF in basal ganglia cerebral infarction is rarely reported. We think that basal ganglia cerebral infarction caused PAF should be associated with central sympathetic nerve

damage triggered abnormal vagus nerve tension, which induced increased cardiac vagus nerve tension and PAF occurred. Previous studies have shown that the basal ganglia contain new striatum, substantia nigra, hypothalamic nucleus and globus pallidus. The dopamine-rich neurons are mainly located in the substantia nigra, and the nerve fibers are projected onto the striatum. Basal ganglia cerebral infarction could cause those nerves damaged, resulting in dopaminergic neurotransmitter synthesis and decreased secretion, which cause central sympathetic dysfunction, sympathetic nerve enameline (Norepinephrine) synthesis release, decreased plasma norepinephrine level, the significantly increased central vagus hyperthyroidism and acetylcholine (ACh), and finally cause cardiac sympathetic phenomenon [5,6]. In our study of cardiac autonomic nerve function in patients with cerebral infarction complicated with PAF, we found that the criteria of HRV in basal ganglia cerebral infarction group were significantly increased, compared with non-basal ganglia cerebral infarction group, such as SSDN was 148 ms, RMSSD was 65.9 ms and HRV triangle index was 56.9, LF/HF was 2.9 in basal ganglia cerebral infarction group, and the SDNN was 111 ms, the RMSSD was 28.9 ms, the HRV trigonometric index was 45.9, and the LF/HF was 1.32.

We also analyzed the differences of incidence, left ventricular ejection fraction, left atrial diameter and heart rate variability in 1 483 patients with basal ganglia cerebral infarction and non-basal ganglia infarction PAF. We found that the basal ganglia cerebral infarction group with higher PAF and accompanied by significant increases in cardiac vasomotor tension, combined with our findings in clinical studies, senile patients with vascular (basal ganglia cerebral infarction) Parkinson's disease, have frequent PAF and/or severe Sinus bradycardia without levodopa treatment, and the clinical phenomenon can be effectively controlled after the recovery of medication, we believe that the elderly basal ganglia cerebral infarction caused by increased central vagus nerve tension, which is the direct cause of clinical vagus-mediated PAF. The increased central vagus nerve tension caused by elevated Ach levels, Ach on the atrial myocytes ion channel (KAch) accelerates the process of myocardial repolarization, shortened action potential, and then also due to the difference of spatial distribution the atrial myocardium ach choline receptor [7], which further causes increased dispersion of atrial tissue effective refractory period, reduced reentry ring wavelength, atrial muscle conduction velocity heterogeneity, resulting in reentry or micro-reentry AF electrophysiological.

Recent studies have shown that nearly 10% of the VP is caused by middle-aged high blood pressure and cerebral arteriosclerosis induced basal ganglia. Kaufmann study shows that almost all VP patients have autonomic dysfunction, manifested as sweating, salivation, intractable constipation, sympathetic dysfunction caused by orthostatic hypotension, limb circulatory disorders, urinary frequency, urinary retention and sexual desire Drop and so on. Goldstein reports that 40% of VP patients have orthostatic hypotension, the possible mechanism is that the cardiac sympathetic, cardiac-vagus and sympathetic pressure reflex disorders caused damage to sympathetic and vagus nervous system [8]. Dennis and Li used PET6-18F-fluorodopamine sympathetic tracer imaging technique to confirm the decrease of sympathetic nerve density and heterogeneity of sympathetic nerve distribution in VP patients [9]. Oliveira reported that elderly patients with positive vertical tilt result in an increased vagus nerve tension with PAF patients [10]. Fedorowski also reported a significant increase in the incidence of AF in patients with hypertension and orthostatic hypotension [11]. Both previous studies and our studies suggest that senile basal ganglia infliction causes central sympathetic nerve injury, which is the direct reason of increased central cardiac vagus nerve tension caused PAF.

In summary, elderly patients with basal ganglia infraction have higher incidence of PAF. The increased sympathetic nerve nucleus injury and increased vagus nerve tension in basal ganglia are the direct reason of PAF caused by abnormal cardiac vagus nerve tension. It is suggested that PAF may be indications of supplemental sympathetic neurotransmitters or cardiac vagus nerve therapy.

Conflict of interest statement

We declare that we have no conflicts of interest.

Acknowledgments

This work was funded by Shanghai Health and Family Planning Commission Youth Fund to Wenbo Cheng (20144Y0116).

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