Clinics in Stroke

Research Article
Published: 29 Jul, 2019

# Basilar Artery Atherosclerosis and Small Vessel Arteriolosclerosis: Different Between Acute and Silent Pontine Infarctions

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## Abstract

**Background:** Pontine infarctions could be categorized as Acute Pontine Infarctions (APIs) and Silent Pontine Infarctions (SPIs). APIs are further classified as Paramedian Pontine Infarction (PPI) and Small Deep Pontine Infarction (SDPI) according to lesion locations. Previously both SPI and SDPI were attributed into small vessel arteriolosclerosis. However, with High-Resolution Magnetic Resonance Imaging (HR-MRI), some studies reported a high prevalence of basilar atherosclerosis among SDPI just like PPI. In this study we aimed to evaluate the basilar arteries of SPIs and APIs with HR-MRI, and compare their underlying vasculopathy.

**Methods:** Participants with API, SPI and healthy subjects were recruited and scanned with HR-MRI for the identification of basilar artery atherosclerosis. Prevalence and severity of leukoaraiosis were evaluated on MRI. Prevalence of vascular risk factors, basilar atherosclerosis and leukoaraiosis was compared among three groups.

**Results:** Compared with API patients, more subjects in SPI group had long-term hypertension, periventricular and severe leukoaraiosis which indicated severe arteriolosclerosis, less had diabetes and dyslipidemia. Besides, prevalence of basilar atherosclerosis in SPI group was similar to that of control group, much less than that of API group.

**Conclusion:** Small vessel arteriolosclerosis was the predominant vascular change of SPIs, differently from that of APIs.

**Keywords: Pontine infarction; HR-MRI; Small vessel arteriosclerosis; Atherosclerosis**

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**Received Date**: *18 Jun 2019*
**Accepted Date:** *26 Jul 2019*
**Published Date:** *29 Jul 2019*

***Citation:***
*Li L, Xu Y, Hua T, Xia S-D, Feng C. Basilar Artery Atherosclerosis and Small Vessel Arteriolosclerosis: Different Between Acute and Silent Pontine Infarctions. Clin Stroke. 2019; 1(1): 1001.*



## Introduction

Pontine infarction is a common type of posterior circulation infarction. Acute Pontine Infarctions (APIs) are quite recognizable on Diffusion-Weighted Images (DWI) with typical symptoms such as dizziness, vertigo and nausea [1,2]. On the other hand, some patients have no obvious symptoms and have pontine infarctions identified accidentally; these infarctions were more like cavitations without hyper intensities on DWI, and are regarded as Silent Pontine Infarctions (SPIs) [3-5]. The underlying vasculopathy of pontine infarction has not been clearly elucidated yet. Previously, APIs with different sizes and locations were attributed to different etiologies. Large Paramedian Pontine Infarctions (PPI) which extend to the ventral surface of the pons were attributed to the occlusion of perforator orifices due to atherosclerotic plaques, while the Small Deep Pontine Infarctions (SDPI) were attributed to small vessel arteriolosclerosis, which mainly includes arteriole lipohyalinosis and fibrinoid necrosis, differently from atherosclerosis [6-9]. However, With High-Resolution Magnetic Resonance Imaging (HR-MRI), Klein and our group demonstrated that both PPI and SDPI were related to basilar atherosclerosis, which could obstruct the perforators with or without obvious stenosis of basilar artery, but used to be neglected by other tools especially for SDPI [10,11]. On the other hand, no study evaluated the basilar arteries of patients with SPIs which are attributed to arteriolosclerosis of basilar perforators all along. We assumed that most patients with SPIs might have basilar atherosclerosis just like SDPI but were neglected by common imaging tools. In order to test this assumption, we supplemented a cohort of patients with only SPIs and evaluated their basilar arteries using HR-MRI. In contrast to the data of PPI and SPI (which were both categorized as APIs) in our previous study, we tried to compare their underlying vascular changes.

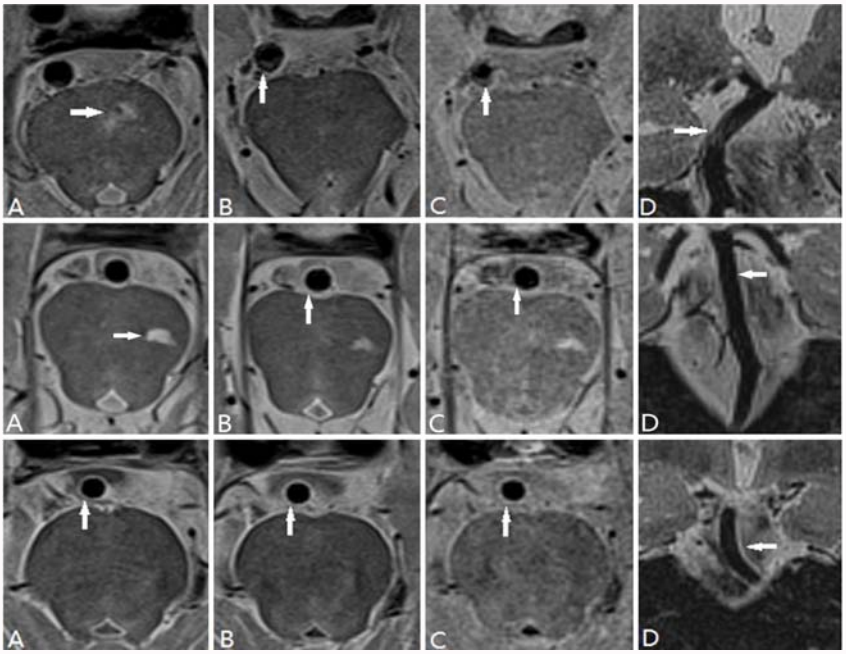


**Figure 1: BA HR-MRI images of API, SPI and control group:** The brain stems and basilar arteries of subjects from API, SPI and control groups were respectively illustrated in row 1-3. The infarcts of API and SPI are shown in proton-density images (A, arrows in row 1, 2). Atherosclerotic plaques of API are shown in proton-density, T2-dark-fluid-spair, and 3D-SPACE images (B-D, arrows in row1). Normal BA walls with no plaque are shown in proton-density, T2-dark-fluid-spair and 3D-SPACE images (B-D arrows in row 2, 3).

## Materials and Methods

This study was based on the patients of Shanghai Tenth People's Hospital. From June 2011 to May 2012, 81 patients with isolated API were consecutively enrolled and assigned to API group. Besides, 30 subjects without any posterior circulation infarcts from January 2012 to March 2012 and 42 subjects with only SPI From June 2012 to January 2013 (both screened from subjects aging from 50 to 80-year-old attending to hospital for health examination with consent to this study) identified by brain MRI were consecutively enrolled and assigned respectively to control and SPI groups. Patients with histories of posterior circulation stroke, atrial fibrillation, arthritis, severe heart failure, vertebral artery stenosis more than 50% identified by color Doppler Ultrasound were all excluded. All subjects were evaluated following the same protocols including: brain MRI to evaluate the presence and types of pontine infarctions, electrocardiogram and echocardiogram to exclude the presence of persistent/permanent atrial fibrillation and mural thrombus, color Doppler Ultrasound to exclude severe vertebral artery stenosis. HR-MRI of basilar artery to evaluate the presence of atherosclerosis. Besides, venous blood was sampled to test the levels of blood glucose, lipid and homocysteine. The histories of hypertension including the duration of hypertension, diabetes, dyslipidemia, smoking and corresponding drug use were recorded. All subjects were scanned by a 3.0 T MR Scanner (Siemens, Germany). The sequences of MRI for the whole brain included T1 and T2-weighted images, Fluid-Attenuated-Inversion-Recovery (FLAIR) and DWI, obtained in the axial plane with a thickness of 5 mm. Protocol of black-blood HR-MRI for basilar artery included proton-density-TSE (TR/TE=3290/16, slice thickness =2 mm), T2-dark-fluid-spair (TR/TE=3000/26, slice thickness =2 mm) and T2-3D-SPACE sequences (TR/TE=1500/250, slice thickness =0.8 mm). API was defined as a focal lesion on pons with hypo intensity on T1-weighted images, hyperintensity on T2-weighted images, FLAIR and DWI, with acute symptoms including dizziness, vertigo, hemiplegia, hemihypesthesia or ataxia, with or without the ventral surface of the pons involved in the lesion. SPI was defined as a small deep cavitated lesion on the pons, 5 to 15 mm in size, with hypo intensity on T1-weighted images and DWI, hyperintensity on T2-weighted images, without corresponding history of stroke and transient ischemic attack, and without dizziness, vertigo and neurological deficits identified neither [12]. The diagnosis of SPI should be based on the exclusion of dilated Virchow-Robin Spaces (VRS), which are more likely to be multiple in one pontine, <3 mm to 5 mm in size, with signal similar to that of cerebral-spinal fluid on MRI sequences, and without hyperintensity boundaries on FLAIR which are in favor of the diagnosis of SPI [12,13]. Basilar artery atherosclerosis was evaluated on HR-MRI, and identified as "normal" when there was no atherosclerotic plaques, no regional or segmental thickness of the vessel wall shown on HR-MRI, "mild stenosis" when the lumen stenosis caused by atherosclerosis was less than 30%, and "stenosis" when the lumen stenosis of basilar artery was more than 30% [11]. Both "mild stenosis" and "stenosis" were regarded as positive results of HR-MRI. Besides, periventricular and deep leukoaraiosis, i.e., white matter hyper intensities as an important phenotype of small vessel disease often found coexisting with infarctions, was assessed respectively and scored as 0 to 3 according to Fazekas' scale in which grade 0 was defined as no hyper intensities in both periventricular and deep regions, grade 1 was defined as scattered hyper intensities, grade 2 and 3 were defined as emerged hyper intensities and diffuse involvement of the entire region. Grade 2 and 3 were both identified as advanced leukoaraiosis [14,15]. All images were analyzed by two readers blinded to the clinical information. The discrepancies about the result of HR-MRI and the scores of leukoaraiosis between 2 readers were resolved by a visual consensus. All data were analyzed with SPSS 18.0. Categorical data including sex, the prevalence of hypertension, diabetes, dyslipidemia, hyperhomocysteinemia, smoking and etc. were shown as % (n), and compared between two groups using

**Table 1:** Baseline characteristics of three groups.

| | SPI (n=42) | Control (n=30) | P (*VS.* SPI) | API (n=81) | P (*VS.* SPI) |
|---|---|---|---|---|---|
| Age, years | 67.10 ± 6.51 | 55.83 ± 5.49 | 0 | 65.21 ± 7.28 | 0.161 |
| Male, % (n) | 59.5 (25) | 66.7 (20) | 0.537 | 66.7 (54) | 0.433 |
| Hypertension, % (n) | 88.1 (37) | 30.0 (9) | 0 | 80.2 (65) | 0.273 |
| Duration ≥ 10 years, % (n) | 35.7 (15) | 13.3 (4) | 0.034 | 16.0 (13) | 0.014 |
| Diabetes, % (n) | 11.9 (5) | 6.7 (2) | 0.46 | 30.9 (25) | 0.02 |
| Dyslipidemia, % (n) | 47.6 (20) | 43.3 (13) | 0.719 | 70.4 (57) | 0.013 |
| Hyperhomocysteinemia, % (n) | 64.3 (27) | 30.0 (9) | 0.004 | 48.1 (39) | 0.089 |
| Current smoking, % (n) | 28.6 (12)) | 23.3 (7) | 0.619 | 29.6 (24) | 0.903 |

**Table 2:** Basilar atherosclerosis and leukoaraiosis of three groups.

| | SPI (n=42) | Control (n=30) | P (VS. SPI) | API (n = 81) | P (VS. SPI) |
|---|---|---|---|---|---|
| Basilar atherosclerosis, % (n) | 16.7 (7) | 10.0 (3) | 0.506 | 67.9 (55) | 0 |
| Mild stenosis, % (n) | 14.3 (6) | 10.0 (3) | 0.857 | 35.8 (29) | 0.012 |
| Stenosis ≥ 30%, % (n) | 2.4 (1) | 0.0 (0) | 1 | 32.1 (26) | 0 |
| Periventricular leukoaraiosis, % (n) | 83.3 (35) | 23.3 (7) | 0 | 63.0 (51) | 0.019 |
| Deep leukoaraiosis, % (n) | 88.1 (37) | 26.7 (7) | 0 | 81.5 (66) | 0.346 |
| Advanced leukoaraiosis, % (n) | 59.5 (25) | 6.7 (2) | 0 | 38.3 (31) | 0.025 |

$\chi^2$ test and Fisher's exact test. Measurement data such as age were listed as average ± standard deviation and compared between two groups using Student's t test. A value with P<0.05 was considered to have statistical significance. All procedures were approved by the Institutional Review Board of our hospital, and written informed consent was obtained from every participant.

## Results

### The baseline characteristics of three groups

Compared with control group, subjects of SPI groups were relatively older, with much higher prevalence of hypertension and hyperhomocysteinemia (P<0.01). Subjects of API and SPI groups were similar in age, sex, the prevalence hypertension and smoking. However, more subjects of SPI groups (35.7%) had more than 10 years of hypertension, with lower prevalence of diabetes and dyslipidemia than those of API group (P<0.05). Details of the characteristics were listed in Table 1.

### Basilar atherosclerosis and leukoaraiosis of three groups

Seven of the 42 subjects (16.7%) in SPI group, 3 of the 30 subjects (10%) in control group and 55 of the 81 patients in API group were identified to have basilar atherosclerosis on HR-MRI. The positive rate in SPI and control groups were similar (P>0.05) and relatively low, much lower than that in API group (P<0.01). The samples of HR-MRI for three groups were illustrated in Figure1. On the other hand, SPI group had rather high prevalence of both periventricular (83.3%) and deep leukoaraiosis (88.1), with 25 of the 42 subjects (59.5%) identified to have advanced leukoaraiosis, much higher than those of and control groups (P<0.01). Besides, periventricular leukoaraiosis and advanced leukoaraiosis were also more common in SPI group than those in API group (P<0.05). Results of the above-mentioned comparisons were listed in Table 2.

## Discussion

This study showed that, compared with APIs which had rather high prevalence of basilar atherosclerosis, only a small part of SPIs had basilar atherosclerosis identified on HR-MRI. Besides, SPIs had higher load of small vessel arteriolosclerosis than APIs. These results suggested that APIs and SPIs might have different underlying vascular changes, i.e., basilar atherosclerosis and small vessel arteriolosclerosis. The vasculopathy underlying pontine infarction has been studied for several decades. For the two subtypes of APIs, i.e., PPI and SDPI, PPI is a typical type of infarction caused by perforator atherosclerosis as proven by various studies while SDPI was usually assigned to small vessel arteriolosclerosis just like SPIs until the use of HR-MRI which showed that most SDPIs had basilar atherosclerosis identified and suggested a high prevalence of basilar perforator atherosclerosis [7,10,16]. However, we neglected SPIs in the first stage of our HR-MRI study and only focused on APIs. In order to remedy this limitation, in the subsequent study, subjects with only SPIs were recruited. And the comparison showed that APIs and SPIs were different in various aspects including vascular risk factors, prevalence of leukoaraiosis and basilar atherosclerosis. We first analyzed the vascular risk factors of three groups. Compared to patients with APIs, more subjects in SPI group had long-term hypertension, less had diabetes and dyslipidemia. Besides, SPI group had higher level of homocysteine than control group. Diabetes and dyslipidemia are both strong risk factors for atherosclerosis. Their roles in arteriolosclerosis are not clearly classified [17]. Some studies even suggested that dyslipidemia was a protector against small vessel arteriolosclerosis [18-20]. Homocysteine is a newly established vascular risk factor for both atherosclerosis and small vessel arteriolosclerosis, with the latter associated with high level of homocysteine more strongly [21]. Hypertension is regarded as the basis of small vessel arteriolosclerosis and also an important risk factor for artery atherosclerosis [22]. Fisher suggested that long-standing hypertension might tend to result in small vessel arteriolosclerosis instead of atherosclerosis [9]. In a word, subjects with SPIs seemed to have more vascular risk factors associated with small vessel arteriolosclerosis, while in API group, risk factors associated with atherosclerosis were dominant. The evaluation about leukoaraiosis and basilar atherosclerosis further verified the results about risk factors. Leukoaraiosis is related

to the chronic and incomplete ischemia caused by small vessel arteriolosclerosis, and is regarded as a typical type of small vessel disease [15,23,24]. The results of this study showed that leukoaraiosis especially severe leukoaraiosis was more common in SPI group. It suggested more severe arteriolosclerosis in SPI group than that in API group. Besides, the results of HR-MRI showed that only a small part of subjects in SPI group had basilar atherosclerosis identified, with the prevalence similarly to that in control group and much lower than that in API group. Anyway, the results of radiological evaluation showed that the main type of vasculopathy was different in API and SPI groups. Compared with patients of API group most of whom had basilar atherosclerosis identified by HR-MRI, more subjects with SPIs had severe small vessel arteriolosclerosis other than basilar atherosclerosis. This was the first study about the underlying vasculopathy of APIs and SPIs evaluated by HR-MRI. It demonstrated that, differently from APIs, only a small part of patients with SPIs had basilar atherosclerosis, with small vessel arteriolosclerosis as their predominant vasculopathy. Based on this cross-sectional study with limited sample size especially for SPI and control groups, we couldn't make further analysis about the role of the two types of vasculopathy in the pathogenesis of pontine infarction. However, considering that small vessel arteriolosclerosis and atherosclerosis had different roles in ischemic changes with the former associated with chronic ischemia more strongly, it's reasonable to speculate that the formation of SPIs was differently from that of APIs which were associated with acute ischemia after atherosclerotic occlusion [15]. In the future, more prospective and basic studies should be designed to prove it.

## Acknowledgement

This research was supported by grants from the National Natural Science Foundation of China (No. 81600393) and the Zilong Mountain Young Talent Program of ZJU4H.

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