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Clinical Study

Posterior communicating artery hypoplasia as a risk factor for acute ischemic stroke in the absence of carotid artery occlusion

Yu-Ming Chuang [a,b,c,d], Chih-Yang Liu [a,b], Po-Jung Pan [c], Ching-Po Lin [d,*]

[a] Department of Neurology, Tao-Yuan General Hospital, Tao-Yuan City, Tao-Yuan, Taiwan
[b] Taipei Veterans General Hospital, Taipei, Taiwan
[c] School of Medicine, National Yang-Ming University, Tao-Yuan City, Taiwan
[d] Institute of Neuroscience, Institute of Biomedical Imaging and Radiological Sciences, National Yang-Ming University, 155 Li-Nong Street, Pei-Tou, Taipei 112, Taiwan

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Abstract

Posterior communicating artery (PCoA) hypoplasia is a fetal variant of the Circle of Willis. According to angiograms and autopsy reports, this congenital variation is found in 6–21% of the general population. PCoA hypoplasia only becomes a risk factor for ischemic stroke in the presence of ipsilateral internal carotid artery (ICA) occlusion. The aim of our study was to determine the role of PCoA hypoplasia in acute ischemic stroke in the absence of ICA occlusion. We examined 310 acute ischemic stroke patients (mean age ± standard deviation; 68.9 ± 15.6 years). Cerebral magnetic resonance angiography was performed within 72 hours of ischemic stroke onset. For comparison, a risk factor-matched control group was recruited. Conditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) to estimate the independent effect of potential risk factors. The overall incidence of PCoA hypoplasia in our experimental group was 19.35% ($n = 60$), which was significantly higher than in the control group (8.20%, $n = 22$, $p = 0.036$, OR, 3.21; 95% CI, 1.43–9.62). The most common ischemic event was ipsilateral thalamic lacunar infarctions with or without occipital lobe involvement. Based on our results, PCoA hypoplasia appears to be a contributor to the risk of ischemic stroke, even in the absence of ICA occlusion. This risk is especially pronounced for strokes involving arteries that penetrate the thalamus.

Keywords: Circle of Willis; MR angiogram; Penetrating artery; Posterior communicating artery; Posterior communicating artery hypoplasia; Thalamus

1. Introduction

The posterior communicating artery (PCoA) is a principal collateral circulation pathway and the source of numerous penetrating arteries that supply the ventral lateral and dorsomedial thalamic nuclei, as well as the lateral aspect of the thalamic pole, tuber cinereum, mamillary bodies, and cerebral peduncle.[1] PCoA hypoplasia is a congenital variant of the circle of Willis characterized by a narrow, underdeveloped PCoA with restricted blood flow. According to angiograms and autopsy reports, it occurs in 6–21% of the general population[1] and is regarded as a predisposing factor in hemispheric low-flow infarcts in carotid occlusive disease.[2,3] However, both Gerstner et al.[3] and Schomer et al.[4–6] suggest that PCoA hypoplasia is, in and of itself, asymptomatic except in the presence of an ipsilateral internal carotid artery (ICA) stenosis.[3] We propose that PCoA hypoplasia remains a risk factor for ischemic stroke, even without an accompanying ICA stenosis.

Today, PCoA hypoplasia is readily detected on MR angiograms, while diffusion-weighted imaging (DWI) can be used to localize the corresponding acute ischemic lesions within the first hours of ischemia, making adequate clinical–radiological correlation possible. In this study, analysis

* Corresponding author. Tel.: +886 3 369 9721x3235; fax: +886 3 369 7118.
E-mail address: chuangymmd@hotmail.com (C.-P. Lin).

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of topographic and etiological patterns of acute ischemic stroke was conducted in patients with PCoA hypoplasia without ICA occlusion.

2. Patients and methods

We selected 379 patients who presented consecutively between January 2006 and October 2006 following a spontaneous ischemic stroke. Of these, we included 310 patients (210 men, 100 women; aged 68.9 ± 15.6 years); 69 patients were excluded because of MRI incompatibility (58 patients were unable to tolerate MRI and 11 had pacemakers). Also excluded were patients with traumatic cervical vascular dissection-related cerebral infarction.

Ischemic strokes were scored according to the National Institutes of Health Stroke Scale (NIHSS) on days 1, 15, 30 and 60 of morbidity.[3] Cardiovascular tests, including electrocardiograms and transthoracic echocardiograms, were also conducted on each patient. Additionally, transesophageal echocardiography was performed in cases of atrial fibrillation and suspected organic heart disease. Subtypes of acute ischemic stroke were determined according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria[8] for every included subject.

After completing a risk factor survey, a control group (200 men, 110 women; aged 64.2 ± 16.5 years, range 54–88 years) was selected from a migraine trial. Although migraine is a risk factor for stroke, a history of migraine is not a risk factor for developing an ischemic stroke in the elderly[9] or those older than 50 years.[10] Furthermore, the similar age of patients in our study (64.2 ± 16.5 years old) justified the use of this control population.

Each stroke subject was paired with an age, sex, and vascular risk factor-matched control (Table 1). Risk factors were matched as follows. When the vascular risk factors of the stroke victim remained undetermined, they were paired with a healthy age/sex-matched control. When a single vascular risk factor was established for the stroke victim, a risk factor-matched control was selected. When two or more risk factors were identified, a control subject with at least two identical vascular risk factors was selected. Those in the control group underwent a similar MRI protocol for detection of cerebral vascular abnormalities. This study protocol was approved by the Institution Review Board of the Tao-Yuan General Hospital and a signed consent form was obtained from all patients and their relatives.

Table 1
Baseline characteristics

	Total group $n = 310$	Controls $n = 310$
Age range, years	56–87	54–88
Mean age, years	68.9	64.2
Sex (M–F)	210–100	200–110
Medical history		
Hypertension	82	79
Diabetes mellitus	66	68
Atrial fibrillation	15	18
Other cardiac disease	28	26
Hypercholesterolemia	78	81
Oral contraceptives	8	7
Smoking	30	32

Duplex color-coded ultrasonography, cerebral MRI, and magnetic resonance angiography (MRA) (1.5 Tesla system, Picker Edge Eclipse, Picker International, Cleveland, OH, USA) were carried out on every acute ischemic stroke victim within 72 hours of admission. To visualize the circle of Willis, 50 slices were obtained using a 3-dimensional MRA time-of-flight technique (time to repetition, TR, 31 ms; time to echo, TE, 6.9 ms; 2 signals acquired; 20° flip angle; 1.2 mm slice thickness with a 0.6 mm overlap; 100 mm field of view; and a 128 × 128 matrix). These images were reconstructed in transverse oblique planes using a maximum intensity projection algorithm. DWI were obtained in the transverse plane using a single-shot echoplanar, spin-echo pulse sequence with a TR/TE of 6500/107 ms, 1 excitation, and 2 b values (0 and 1000 s/mm^2). The diffusion-gradient pulse duration was 31 ms with a gradient separation of 33 ms and a gradient strength of 2.16 g/cm. The diffusion-gradients were applied simultaneously along the three axes (x, y, and z).

DWI was used to define a corresponding acute ischemic lesion. A distribution and size measurement of DWI hyperintense lesions was used for topographic localization and TOAST classification.[8] We defined a stroke in the territories of the anterior cerebral artery (ACA), middle cerebral artery (MCA) or the posterior cerebral artery (PCA) as a hemispheric stroke, and a brainstem–cerebellar stroke as one in the territories of the vertebral and basilar arteries. An integration of T1-weighted and T2-weighted imaging characters was essential for etiology differentiation.

Diagnosis of acute ischemic stroke was made based on physical examination and cerebral MRI correlation by two board-certified neurologists (YM Chuang and CY Liu). The same MRI protocols were performed on stroke patients and the migraine control group. The results of cerebral MRI and MRA were reviewed by a board-certified neuroradiologist (CH Yang), who was blind to the patient's role in the study. A diagnosis of PCoA hypoplasia was based on the presence of MRA showing either a PCoA of less than 1 mm in diameter or the absence of a PCoA.[6] Because of the limited resolution of MRA, it was sometimes difficult to differentiate PCoA hypoplasia (<1 mm in diameter) from agenesis (absence of the PCoA). Therefore the criteria for hypoplasia we used were a PCoA diameter of <1 mm or an absent vessel. Extracranial ICA stenosis (≥70%) was diagnosed according to the North American Symptomatic Carotid Endarterectomy Trial method.[4,5] Using this method, the presence or absence, of tandem intracranial occlusive disease with ≥70% luminal stenosis, as shown by MRA, was noted for all experimental patients.

We divided the cohort into three subgroups to determine the stroke pattern caused by PCoA hypoplasia. The first

group was the "PCoA hypoplasia plus" group consisting of 12 PCoA hypoplasia patients with tandem intracranial vascular occlusive disease. The second group was the "pure PCoA hypoplasia" group: 48 PCoA hypoplasia patients without tandem vascular morbidity. The third group was the "non-hypoplastic PCoA group" ($n = 250$).

Two-tailed p-values of $\leqslant 0.05$ were considered statistically significant. Statistical Package for the Social Sciences (SPSS) software version 10.0 (SPSS, Chicago, IL, USA) was used for statistical analyses. Conditional logistic regression with univariate analysis was used to calculate ORs and 95% CIs to estimate the independent effects of potential risk factors. Data are reported as mean ± standard deviation (SD).

3. Results

We studied 210 subjects with hemispheric ischemic strokes (136 men, 74 women) aged 59.8 ± 14.7 years (range 54–82 years) and 100 subjects with brainstem/cerebellum ischemic strokes confirmed by MRI (74 men, 26 women) aged 56.8 ± 13.7 years (range 56–88 years). Unilateral PCoA hypoplasia was diagnosed with MRA in 60 subjects (Fig. 1). None of the subjects had bilateral PCoA hypoplasia.

The incidence of PCoA hypoplasia in hemispheric ischemic stroke patients was 19.35% (60/310), which was significantly higher than the control group (8.20%; $n = 22$, $p = 0.036$). Univariate analysis yielded an OR of 3.21 (95% CI, 1.43–9.62). Left-sided (L) preponderance of this anomaly was evident (R:L = 22:38). There were 12 PCoA hypoplasia stroke victims with either tandem extracranial ICA occlusive disease ($n = 6$), intracranial occlusive disease ($n = 4$, MCA = 3, PCA = 1), or another circle of Willis variant (A1 hypoplasia, $n = 1$; anterior communicating artery hypoplasia, $n = 1$).

3.1. Topographic distribution of stroke focus in patients with PCoA hypoplasia

Topographic distribution of stroke in patients with PCoA hypoplasia indicated an association with ipsilateral hemispheric ischemia, especially within the thalamus (77.08%, $n = 37$) (Table 2), or mixed thalamic/occipital lobe (20.83%, $n = 10$) (Fig. 1). The overall incidence of thalamic infarction in the hypoplastic PCoA group was significantly higher than was found for the non-hypoplastic PCoA group (27.2%, $n = 68/250$, $p = 0.021$). Furthermore, the rate of association of PCoA hypoplasia with hemispheric infarction (21.27%; $n = 40$), was significantly higher than its association with brain stem/cerebellar ischemic stroke (10%; $n = 8$, $p = 0.032$) (Table 2). Also, 83.33% of right PCoA hypoplasia (15/18) and 73.33% of left PCoA hypoplasia subjects (22/30) had ipsilateral hemispheric infarctions. The most common event found was an ipsilateral thalamic lacune (85.18%, 23/27). In contrast, this correlation of laterality was absent in the PCoA hypoplasia plus group. Additionally, all PCoA hypoplasia subjects with a contralateral major artery occlusion (ICA, $n = 2$/MCA, $n = 1$/PCA, $n = 1$) developed a contralateral cerebral infarct (Table 3).

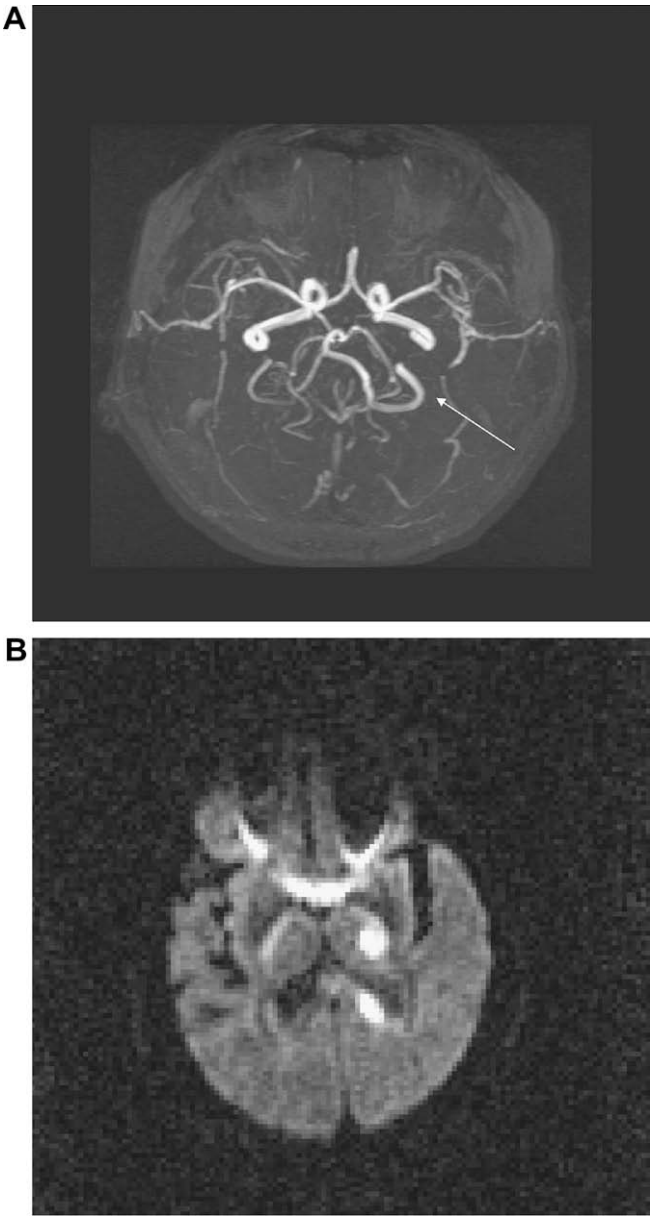

Fig. 1. (A) Cerebral magnetic resonance angiogram of a 53-year-old male with a 10-year history of hypertension, who presented with acute onset of right hemiparesis, hemianesthesia and homonymous hemianopsia. (B) The corresponding MRI (diffusion-weighted imaging) disclosed multifocal hyperintense lesions involving the left thalamus and occipital lobe; which fulfilled the posterior choroidal artery occlusion[11] and TOAST subtype criteria for small-artery artherosclerosis. This image also revealed agenesis of the left posterior communicating artery (arrow). (TOAST = Trial of ORG 10172 in Acute Stroke Treatment).

In the PCoA hypoplasia plus group, 33% of tandem ICA occlusion subjects developed a watershed infarction, which was significantly more frequent than what was found for the pure PCoA hypoplasia group ($p = 0.021$). Furthermore, patients with a tandem intracranial major vascular

Table 2
Topographic distribution of the "pure PCoA hypoplasia" group

Territorial distribution	"Pure PCoA hypoplasia" $n = 48$	"Non-hypoplastic PCoA" $n = 250$
Hemispheric stroke		
ACA	0	16
MCA	1	128
Superior division	0	38
Inferior division	0	42
Striatocapsular division	1	48
PCA	2	38
Watershed	0	18
Thalamic lacune	37	68* ($p = 0.021$)
Brainstem/cerebellar stroke		
VA	5	32
BA	3	62

ACA = anterior cerebral artery; BA = basilar artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; PCoA = posterior communicating artery; "Pure PCoA hypoplasia" group = 48 PCoA hypoplasia patients without tandem vascular morbidity; VA= vertebral artery.

Table 3
Topographic distribution of "PCoA hypoplasia plus" group

"PCoA hypoplasia plus" group ($n = 12$)		Topographic distribution
PCoA hypoplasia plus ICA occlusion (n = 6)		
46 y/o M	Rt PCoAH + Rt ICAO	Rt MCA/PCA watershed
52 y/o F	Rt PCoAH + Rt ICAO	Rt MCA/PCA watershed
55 y/o M	Rt PCoAH +Lt ICAO	Lt thalamic lacune
51 y/o M	Lt PCoAH+Lt ICAO	Lt MCA superior division
46 y/o M	Lt PCoAH + Lt ICAO	Lt thalamic lacune
56 y/o F	Lt PCoAH + Rt ICAO	Rt MCA superior division
PCoA hypoplasia plus intracranial vascular occlusive disease (n = 4)		
65 y/o M	Rt PCoAH + Rt MCAO	Rt MCA striatocapsular
57 y/o M	Lt PCoAH + Rt MCAO	Rt MCA inferior division
55 y/o F	Lt PCoAH + Lt MCAO	Lt MCA striatocapsular
51 y/o M	Lt PCoAH + Lt PCAO	Lt thalamic lacune
PCoA hypoplasia plus another circle of Willis variant (n = 2)		
65 y/o M	Rt PCoAH + Rt A1H	Rt MCA striatocapsular
53 y/o F	Lt PCoAH + AcoAH	Lt thalamic lacune

PCoAH = posterior communication artery hypoplasia; ICAO = internal carotid artery occlusion; MCAO = middle cerebral artery occlusion; PCAO = posterior cerebral artery occlusion; A1H = anterior cerebral artery A1 segment hypoplasia; AcoAH = anterior communication artery hypoplasia; y/o = years old; M = male; F = female; Lt = left; Rt = right.

occlusion were more likely to develop a relevant territorial infarction than a thalamic lacune or a watershed infarct (Table 3).

3.2. PCoA hypoplasia was more frequent among patients with small vessel stroke

A survey of all 310 subjects, using the TOAST classification, found large-artery atherosclerosis in 46, cardioembolism in 63, small-artery occlusion in 152, other causes of stroke in 9, and undetermined causes of stroke in 39 patients. We found that PCoA hypoplasia was significantly more common in patients with small-artery atherosclerosis ($n = 38$; 25%) than in those with large-artery occlusions ($n = 5$; 10.86%, $p = 0.041$), cardioembolism ($n = 4$; 6.34%, $p = 0.031$), or disease of undetermined origin ($n = 1$; 2.56%, $p = 0.028$).

3.3. PCoA hypoplasia-related strokes are associated with lower NIHSS

The mean NIHSS score of the PCoA hypoplasia group ($n = 60$) was significantly lower than that of the non-PCoA hypoplasia group on day of morbidity 1 (10 ± 2.3 vs. 18 ± 6.2; $p = 0.03$), 15 (8 ± 2.5 vs. 12 ± 3.4; $p = 0.02$), 30 (7 ± 1.4 vs. 11 ± 3.9; $p = 0.02$), and 60 (5 ± 1.8 vs. 9 ± 3.8; $p = 0.01$). When comparing stroke type, 30 patients had a first-ever minor stroke, including pure motor stroke (PMS; $n = 3$), pure sensory stroke (PSS; $n = 5$), sensorimotor stroke plus partial visual field defect (SMS + partial visual field defect, $n = 12$), sensorimotor stroke (SMS, $n = 9$), and ataxic hemiparesis (AH; $n = 1$). Furthermore, significantly more patients with PCoA hypoplasia-related stroke (37.5%, $n = 18$) had a transient ischemic attack (TIA) than the non-PCoA hypoplasia stroke patients (15.2%, $n = 38$; $p = 0.03$).

4. Discussion

Based on the results of this small-scale study, we postulate that PCoA hypoplasia, in and of itself, may have a pathophysiological role in stroke. We found that PCoA hypoplasia is associated with a watershed infarction when it coexists with a carotid artery occlusion. This observation supports the hypothesis of Schomer et al.[6]

PCoA hypoplasia also shows a topographic preponderance of ipsilateral thalamic lacunar stroke in the absence of carotid artery occlusion (although the correlation of laterality is abolished in cases of tandem major intracranial artery occlusion), an etiological preponderance of small-artery atherosclerosis, and a correspondingly lower NIHSS score. Our observation of a topographic preponderance of ipsilateral thalamic lacunar stroke in the absence of carotid artery occlusion is novel.

It seems that PCoA hypoplasia predisposes to small vessel infarcts of the thalamus, perhaps via a different mechanism than found in typical lacunar infarctions. We traditionally think of acute occlusions of a single small vessel as leading to lacunar infarction. In contrast, PCoA hypoplasia may predispose to thalamus lacunes via PCoA-related poor regional collaterals.[7,8] That is, PCoA hypoplasia might predispose to "low flow" infarction in thalamic perforating branches that are already diseased in the traditional lacunar manner.

The arterial supply of the thalamus is complicated. Thalamic arteries include the thalamic-subthalamic, thalamogeniculate, polar, and posterior/lateral choroidal arteries, all of which originate from the proximal PCA and anastomoses

in this region. The first interpretation is that due to the close anastomoses, if one has an intact PCoA, then a single branch occlusion might not lead to ischemia due to the critical role the PCoA appears to have in the collateral supply of this region.[11] However, a patient with PCoA hypoplasia would be prone to a symptomatic single branch occlusion. The second explanation is that the thalamus receives blood supply from small perforating branches of the PCoA, which are precariously perfused in the presence of PCoA hypoplasia, predisposing the patient to thalamic infarctions.[1,12,13]

The ipsilateral side correlation of PCoA and stroke was missing in cases of major tandem intracranial artery occlusion.[14,15] In our study, most (75%) angiographic findings of major tandem intracranial artery occlusions indicate the infarct site, regardless of the existence or location of the PCoA. This might occur because a major cerebral artery occlusion has a more catastrophic hemodynamic influence than PCoA hypoplasia.[16] We found that the major arterial occlusion, as disclosed on CT angiography, is always responsible for the ischemic event.[17] Furthermore, Hu et al. have posited that the hemodynamic impact of a cerebral vascular variation is limited to the surrounding brain tissue.[18] Thus, although PCoA hypoplasia has a predisposing role towards acute ischemic events, particularly within the thalamus, its effect is minor compared to that of major tandem intracranial artery occlusions.

Fischer et al. have reported that NIHSS scores are lower in patients with PCoA occlusion than in patients with other territorial morbidity.[19] Duncan et al. have also reported that symptomatic PCoA occlusion is generally clinically tolerable.[20] In our study, nearly one-third of patients with PCoA hypoplasia-related stroke had only a TIA. The others ($n = 30$) had lacunar-like syndromes (PMS, PSS, SMS $\pm$ partial visual field defect, and AH). Most ($n = 21$) had a sensorimotor deficit with or without a partial visual field defect contralateral to the PCoA hypoplasia. These described symptoms are similar to those reported for posterior choroidal artery occlusion.[11] As the posterior choroidal artery originates close to the PCoA, PCoA hypoplasia may predispose to a posterior choroidal artery "low flow" infarction via poor regional collaterals.

Contrary to our argument, van Everdingen et al. posited that one hypoplastic PCoA may be clinically irrelevant if at least one of the other primary collateral pathways is present,[10] while Gerstner et al. suggested that PCoA hypoplasia is asymptomatic unless accompanied by an ipsilateral ICA stenosis.[3] Furthermore, Schomer et al. proposed that posterior communicating artery hypoplasia is a risk factor for ischemic stroke only in case of ipsilateral ICA stenosis.[6] Our result suggests that even in the absence of ICA occlusion, PCoA hypoplasia is an independent contributor to the risk of ischemic stroke.

This relationship is not straightforward, because some bias exists and the clinico-radiologic correlation is inadequate. In our study, DWI was used to eliminate inter-examiner bias. However, because of the limited resolution of MRA, differentiation of PCoA hypoplasia from agenesis was difficult sometimes, and to eliminate this bias, hypoplasia was defined as a PCoA diameter of <1 mm or absence of the PCoA. Even with these criteria, differentiation of a thromboembolic PCoA occlusion from hypoplasia was difficult, despite its extremely low incidence.[7] This is because a thromboembolic PCoA occlusion could send embolic showers into the thalamic perforators and the occipital lobe, which would give a comparable clinical and radiological finding.[20] Furthermore, our sample size was relatively small ($n = 268$) and, given the low frequency of PCoA hypoplasia, any bias may have been enhanced.

A large-scale study will be needed to test the reproducibility of our findings; the study should involve multivariate statistics adjusting for well-established risk factors. Despite these limitations, we believe that PCoA hypoplasias predispose to small vessel infarcts of the thalamus.

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