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Anterior Cerebral Artery A1 Segment Hypoplasia May Contribute to A1 Hypoplasia Syndrome

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Key Words
Anterior cerebral artery · Circle of Willis · MR angiogram · A1 segment hypoplasia · Penetrating artery

Abstract
Anterior cerebral artery A1 segment hypoplasia is an uncommon fetal variant of the circle of Willis. The frequency of this congenital variation is 1–13% as derived from angiograms and autopsy reports. Impaired collateral blood flow through the circle of Willis is a recognized risk factor for ischemic stroke. The A1 segment of the anterior cerebral artery is a principal supplier of anterior collateral blood flow. The aim of our study was to determine whether A1 segment hypoplasia may be responsible for acute ischemic stroke. We consecutively examined 280 acute ischemic stroke patients (aged 66.9 ± 14.2 years). Cerebral magnetic resonance angiography was performed within 72 h of ischemic stroke onset. The overall incidence of A1 variation in our experimental group was 15.0% (n = 42, agenesis/hypoplasia = 18/24), which was statistically higher than in the control group (n = 12). The majority (n = 30, 71.42%) had ipsilateral striatal lacunar infarctions. Based on our results, A1 agenesis/hypoplasia appears to be a risk factor contributing to ischemic stroke, especially to strokes in arteries penetrating the striatal area.

Background and Purpose

Anterior cerebral artery (ACA) A1 segment hypoplasia is an uncommon fetal variant of the circle of Willis. The frequency of this congenital variation is 1–13% as derived from angiograms and autopsy reports [1]. A1 segment hypoplasia, as a non-competent part of the circle of Willis, is regarded as a predisposing factor in hemispheric low-flow infarcts in carotid occlusive disease [2–4]. Anatomically, the A1 segment of the ACA is not only a principal collateral circulation pathway, but is also the source of numerous penetrating striatal arteries that supply the anterior hypothalamus, septum pellucidum, and the anterior and inferior portions of the corpus striatum. In the absence of carotid occlusion, we questioned whether A1 segment hypoplasia is an independent contributor to the risk of stroke.

Today, A1 hypoplasia is readily detected on magnetic resonance (MR) angiograms. Diffusion-weighted imaging (DWI) can be used to localize the corresponding acute ischemic lesions within the first hours, making adequate clinico-radiological correlation possible. In this study, analysis of topographic and etiological patterns of acute ischemic stroke was conducted in patients with A1 segment hypoplasia.

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Subjects and Methods

From January 2005 to September 2006, we consecutively recruited 280 patients (191 men, 89 women) aged 66.9 ± 14.2 years (range 36–88) admitted to the Department of Neurology, Tao-Yuan General Hospital, with a history or signs of acute ischemic stroke (average frequency of hospital admission, 13.3 subjects/month). Diagnosis of acute ischemic stroke was made based on physical examination and cerebral MRI correlation (by two board certified neurologists, Y.M. Chuang and C.Y. Liu). Scores on the National Institute Health Stroke Scale (NIHSS) were recorded on the 1st, 15th, 30th and 60th day of morbidity [5].

To determine the stroke pattern caused solely by A1 segment hypoplasia, we excluded patients with (a) traumatic cervical vascular dissection-related cerebral infarction, (b) morbid cerebral MR angiography with extracranial ICA stenosis ≥70% according to the North American Symptomatic Carotid Endarterectomy Trial method [6], (c) tandem intracranial occlusive disease with proximal MCA stenosis ≥70% on MR angiography, and (d) other tandem circle of Willis variations.

This study protocol was approved by the Institution Review Board of the Tao-Yuan General Hospital. A signed informed consent was obtained from all patients and their relatives.

Cerebral MRI and MR angiograms (1.5 Tesla system, Picker Edge Eclipse, Picker International, Cleveland, Ohio, USA) were carried out on every acute ischemic stroke victim within 72 h of admission. To visualize the circle of Willis, 50 slices were obtained using a three-dimensional MR angiography time-of-flight technique (TR 31 ms; TE 6.9 ms; 2 signals acquired; 20° flip angle; 1.2-mm slice thickness with a 0.6-mm overlap; 100-mm FOV, and a 128 × 128 matrix). These images were reconstructed in transverse oblique planes using a maximum intensity projection algorithm. Diffusion-weighted images were obtained in the transverse plane using a single-shot echoplanar, spin-echo pulse sequence with a repetition time/echo time of 6,500/107 ms, 1 excitation, and 2 b values (0 and 1,000 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).

Results of cerebral MR imaging and MR angiograms were reviewed by a board certified neuroradiologist (C.H. Yang), blind to the subjects' status within the study protocol. The diagnosis of A1 segment hypoplasia of the ACA was based on the MR angiograms showing A1 segments <1 mm in diameter or the absence of A1 segments [7].

Subtypes of acute ischemic stroke were determined according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria [8]. Cardiovascular testing, including electrocardiogram and transthoracic echocardiogram, was done in each subject. Transesophageal echocardiography was performed in cases of atrial fibrillation and transthoracic echocardiogram in suspected organic heart disease (n = 11). Duplex color-coded ultrasonography, cerebral MR imaging, and MR angiography were performed within 72 h of hospitalization. Cerebral MR imaging was also performed in every control subject. The control group was recruited from a migraine study group at the Tao-Yuan General Hospital. Cerebral MR angiography was conducted to verify vascular abnormality. After completing a risk factor survey, a control group (190 men, 90 women; aged 68.2 ± 15.2 years, range 30–88) was selected and matched for age/sex and vascular risk factors. When the vascular risk factors of the stroke victim remained undetermined, a healthy age/sex-matched control subject was enrolled. When a single vascular risk factor was established for the stroke victim, a risk factor-matched control was selected. When more than two risk factors were identified, a control subject with at least two identical vascular risk factors was selected.

Data Analysis

Two-sided p values <0.05 were considered statistically significant. SPSS software (Version 10.0, SPSS Inc., Chicago, Ill., USA) was used for statistical analyses.

Results

Thirty-two patients were excluded (30 with at least one ICA stenosis ≥70%, and 2 with traumatic cervical dissection related infarction) and 280 patients (191 men, 89 women) with a history or signs of acute ischemic stroke were included.

There were 198 hemispheric ischemic strokes (108 men, 66 women) aged 56.5 ± 15.8 years (range 36–80) and 82 brainstem/cerebellum ischemic strokes (83 men, 23 women) aged 54.8 ± 14.5 years (range 38–88), which were confirmed by MRI. A1 segment hypoplasia was diagnosed with MR angiography in 49 subjects (agenesis/hypoplasia = 20/29) (fig. 1). The global incidence of ACA A1 segment hypoplasia was 17.5%, which was significantly higher than in the control group (4.28%; n = 12; p = 0.023). Left-sided preponderance of this anomaly was evident (R:L = 14:28).

Accordingly, we excluded 7 patients with extracranial ICA occlusive disease (n = 4), tandem intracranial occlusive disease (n = 2), and another circle of Willis variant (Pcom hypoplasia; n = 2). Thus, we analyzed the ischemic lesion pattern in the remaining 42 patients (33 men, 9 women; mean age 63.5 ± 8.6 years).

Topographic Distribution of Stroke in Patients with A1 Segment Hypoplasia

Topographic distribution of stroke in patients with A1 segment hypoplasia indicated an association with ipsilateral hemispheric ischemia, especially within the striatum (76.2%, n = 38). The rate of association of A1 hypoplasia with hemispheric infarction was 19.2% (n = 38), which was significantly higher than the association of A1 hypoplasia with brainstem/cerebellar ischemic stroke, at 4.87% (n = 4) (p value: 0.012) (table 1). In addition, 71.4% of right A1 hypoplasia (10/14) and 64.3% of left A1 hypoplasia subjects (18/28) exhibited ipsilateral hemispheric infarctions.

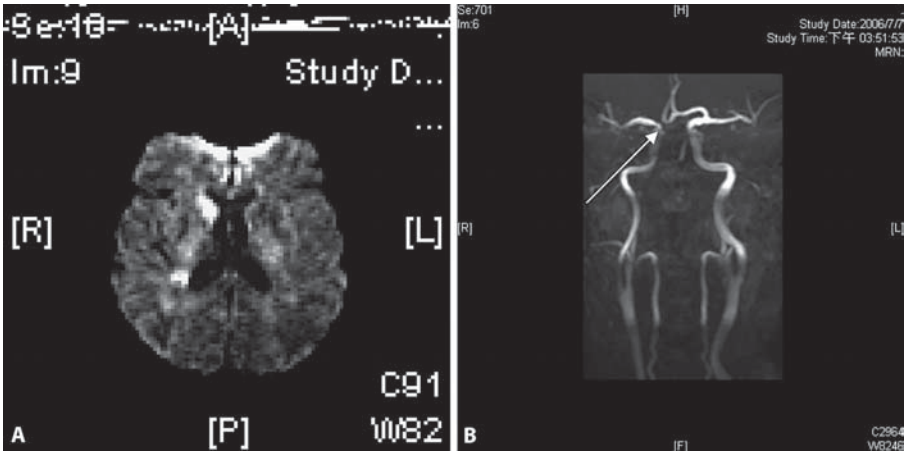

Fig. 1. 63-year-old male with a 5-year history of hypertension, who developed acute onset of left hemiparesis. **A** The corresponding brain MRI (DWI) disclosed multiple infarcts involving the right caudate nucleus with sizes <1.5 cm, which fulfilled the TOAST subtype criteria of small-artery atherosclerosis. **B** Cerebral MR angiogram disclosed agenesis of the A1 segment of the ACA (arrow).

Table 1. Incidence of A1 hypoplasia

	A1 hypoplasia	p value
Stroke patients (n = 280)		
Hemispheric ischemia (n = 198)	38	
Brain stem/cerebellar ischemia (n = 92)	4	0.012
Control subjects (n = 280)	12	0.023

TOAST Subtype Distribution of Stroke in Patients with A1 Segment Hypoplasia

Regarding subtype distribution, 83.3% (n = 35) were classified as having small-artery atherosclerosis. A survey of our 280 subjects using the TOAST classification found large-artery atherosclerosis in 42 subjects, cardioembolism in 62, small-artery occlusion in 122, other causes of stroke in 6, and undetermined causes of stroke in 48 subjects. A1 hypoplasia arose in 28.7% (n = 35) of cases with small-artery atherosclerosis, 3.22% of those with cardioembolism (n = 2), 9.52% of those with large-artery occlusion (n = 4), and 2.08% of those with disease of undetermined origin (n = 1).

A1 Segment Hypoplasia-Related Stroke Associated with Lower NIHSS

In acute ischemic stroke subjects, the mean NIHSS score of patients with A1 segment hypoplasia was significantly lower (i.e., 8 ± 2.4, 6 ± 2.1, 5 ± 1.9, 3 ± 1.2 on the 1st, 15th, 30th and 60th day of morbidity, respectively) than the global NIHSS score for all 280 subjects (15 ± 5.6, p = 0.03; 12 ± 4.1, p = 0.02; 10 ± 3, p = 0.02; 9.8 ± 3.2, p = 0.01). Nearly half of the patients with A1 hypoplasia-related stroke (47.6%, n = 20) had only a transient ischemic attack (TIA). The others (n = 22) had a first-ever minor stroke, including pure motor stroke (PMS; n = 4), pure sensory stroke (PSS; n = 6), sensorimotor stroke (SMS; n = 11), and ataxic hemiparesis (AH; n = 1). By contrast, the global frequency of TIA was only 17.1% (n = 48, p = 0.03).

Discussion

We postulate a pathophysiological role for A1 segment hypoplasia based on the results of this small-scale study. Subjects with A1 segment hypoplasia have a (1) topographic preponderance of ipsilateral hemispheric stroke, (2) etiological preponderance of small-artery atherosclerosis, and (3) a correspondingly lower NIHSS score.

Our observation of a topographic preponderance of ipsilateral hemispheric ischemic stroke is partially consistent with the findings of John et al. [9]. Unilateral defects in the circle of Willis may contribute to the development of ipsilateral hemispheric borderline stroke. Patients with such a defect may have intact contralateral collateral circulation [10].

Our observation of the etiological preponderance of small-artery atherosclerosis was de novo. The majority (83.33%) of A1 segment hypoplasia-related strokes were associated with small vessel occlusion, especially within the striatum. One possible explanation is poor collateral capacity that would render arteries penetrating the striatum vulnerable to ischemic attack [11]. On the basis of the grading system of Brucker et al. [12], patients with A1

segment hypoplasia have impaired collateral circulation. Wang et al. [14], Kang et al. [11] and Caplan and Hennerici [13] posit that thromboembolism clearance is poor within the striatum with defective collateral circulation.

Our observation that A1 segment hypoplasia is associated with lower NIHSS scores supports the findings of Fischer et al. [15]. NIHSS scores were found to be lower in patients with A1 occlusion than in patients with other territorial morbidity. Wijman et al. [16] also reported that symptomatic A1 segment occlusion was clinically tolerable. In our study, nearly half of the patients with A1 hypoplasia-related stroke had only a TIA. The others (n = 22) had lacunar syndromes (PMS, PSS, SMS, and AH). The majority (n = 21) had a sensorimotor deficit contralateral to the A1 hypoplasia. On the basis of the above-mentioned observations, we would like to define a syndrome of A1 segment hypoplasia as a tolerable, sensorimotor deficit contralateral to the A1 segment hypoplasia.

Contrary to our argument, van Everdingen et al. [10] have posited that one hypoplastic A1 segment may be clinically irrelevant if one of the other primary collateral pathways is present, while Gerstner et al. [3] suggest that A1 hypoplasia is asymptomatic unless accompanied by a contralateral ICA stenosis. Schomer et al. [7] proposed that posterior communicating artery hypoplasia rather than A1 segment hypoplasia is a risk factor for ischemic stroke. Our result suggests that, in the absence of ICA occlusion, A1 hypoplasia could also be an independent contributor to risk of ischemic stroke.

This relationship is not straightforward due to the fact that some bias exists and the clinico-radiological correlation is inadequate. In our study, DWI was used to eliminate inter-examiner bias. Second, because of the limited resolution of MR angiography, differentiation of A1 segment hypoplasia from agenesis was difficult in some instances. In order to eliminate this bias, hypoplasia was defined as an A1 segment diameter <1 mm or absent (invisible). Third, the sample size of our study was relatively small (n = 280). Given the low frequency of A1 hypoplasia, bias may be enhanced. A large-scale study will be needed to test the reproducibility of our findings. Despite these limitations, we believe that hemispheric ischemic stroke associated with hypoplasia of the A1 segment is a real entity that deserves greater attention.

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