Screening for intracranial aneurysms? Prevalence of unruptured intracranial aneurysms in Hong Kong Chinese

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OBJECTIVE The objective of this study was to generate data on the local prevalence of unruptured intracranial aneurysms (UIAs) in asymptomatic Hong Kong Chinese individuals. First-degree relatives of patients with aneurysmal subarachnoid hemorrhage (aSAH) were recruited as surrogates of the general population and to explore the potential role of screening in this locality.

METHODS The authors identified first-degree relatives of consecutive patients with subarachnoid hemorrhage from a ruptured aneurysm who were admitted to a university hospital in Hong Kong from June 2008 to December 2010. Magnetic resonance angiography (MRA) was the imaging modality used to screen the cerebral vasculature of these asymptomatic individuals. If MRA showed abnormal findings, CT angiography was performed to confirm the MRA findings.

RESULTS In total, 7 UIAs were identified from the 305 MR angiograms obtained. The prevalence of UIAs in first-degree relatives of patients with aSAH in the Hong Kong Chinese population was 2.30% (95% CI 1.02%–4.76%). This percentage was lower than the prevalence rate of 3.2% from a meta-analysis of the literature. The sizes of the UIAs detected ranged from 1.4 mm to 7.5 mm; 85.7% of the UIAs detected in this study were < 5 mm, in contrast to 66% noted in the literature. One of the UIAs identified underwent endovascular stent placement with a flow diverter. None of the UIAs identified ruptured or became symptomatic during a median follow-up period of 3.5 years.

CONCLUSIONS The prevalence of UIAs in first-degree relatives of patients with aSAH in the Hong Kong Chinese population was lower than that in Caucasians. At the same time, most of the UIAs detected in this study were small (85.7% were < 5 mm, vs 66% in a meta-analysis). With a similar incidence of aSAH in Hong Kong (7.5 per 100,000 person-years) as compared with data cited in the literature, the hypothesis that UIA rupture risk size threshold is different in Chinese patients should be further investigated.

<http://thejns.org/doi/abs/10.3171/2015.4.JNS142938>

KEY WORDS prevalence; unruptured intracranial aneurysm; Chinese; screening; Hong Kong; vascular disorders; subarachnoid hemorrhage; first-degree relative

RUPTURED intracranial aneurysms with subarachnoid hemorrhage (SAH) have high mortality and morbidity rates and affect relatively young people.¹⁴ On an individual level, aneurysmal SAH (aSAH) can cause a lot of anxiety within a family.¹¹ On a public health level, it brings a considerable socioeconomic burden to society.¹² With the increased accessibility of noninvasive imaging with higher resolution, earlier detection of unruptured intracranial aneurysms (UIAs) in asymptomatic individuals in the general population is more common. At the same time,

the emergence of data on therapies such as endovascular coiling and pipeline stents provides more options with acceptable risks in the treatment of UIAs. It is not uncommon for family members to ask if they could possibly harbor an aneurysm as well, and whether they need screening. However, the role of screening has yet to be justified. Ninety-five percent of the Hong Kong population is Chinese, and no previous epidemiological study has focused on the incidence of UIAs in Hong Kong Chinese.¹⁹ These data could guide us in counseling family members with aSAH by of-

ABBREVIATIONS ACoA = anterior communicating artery; aSAH = aneurysmal SAH; CTA = CT angiography; ICA = internal carotid artery; MRA = MR angiography; SAH = subarachnoid hemorrhage; UIA = unruptured intracranial aneurysm; VA = vertebral artery.

SUBMITTED December 27, 2014. **ACCEPTED** April 7, 2015.

INCLUDE WHEN CITING Published online October 16, 2015; DOI: 10.3171/2015.4.JNS142938.

fering screening or follow-up management. It could also have public health implications and guide future resource allocation and service development in Hong Kong.¹⁹

Therefore, our aim in this study was to generate data on the local prevalence of UIAs in first-degree relatives of patients with ruptured intracranial aneurysms and to explore the potential role of screening for first-degree relatives in our locality.

Methods

The study was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee and supported by a direct grant for research from the Chinese University of Hong Kong. Informed consent was obtained from participants and the study conformed to the Declaration of Helsinki. We identified first-degree relatives of consecutive patients with SAH from ruptured aneurysms admitted to a university hospital in Hong Kong (Prince of Wales Hospital) from June 2008 to December 2010.

Screening MRI was performed on a 3-T MRI machine (Achieva TX, Philips Medical Systems) using a standard head coil. Three-dimensional MR angiography (MRA) time-of-flight sequence of the whole brain was acquired using the following parameters: TR 23 msec, TE 3.5 msec, FOV $200 \times 200 \times 56 \text{ mm}^3$, and resolution $0.4 \times 0.6 \times 0.7 \text{ mm}^3$. To complete the clinical scan, axial T1-weighted and T2-weighted, and coronal FLAIR sequences were additionally acquired in 5-mm-thick sections. In addition, confirmatory CT scans were performed on a 64-slice CT scanner (Lightspeed VCT, GE Healthcare). CT angiography (CTA) covering the region of the circle of Willis arteries was acquired in helical mode without tilting at 120 kV, 550 mA, and 0.4-sec rotation, and with the assistance of bolus tracking of intravenously injected contrast (70 ml Omnipaque 300, 3–3.5 ml/sec). Axial images were reconstructed at 0.625-mm slices and used as source images.

MRA data were viewed as source images in multiplanar views, and in angiographic mode generated via maximal intensity projection. Scans were reviewed together by at least 2 neuroradiologists (D.Y.W.S., J.M.A., or T.C.Y.C.), and discrepancies were resolved by consensus. If MRA showed suspicious findings, CTA was performed to confirm the MRA findings.

In this study, MRA was used as the screening method of choice because it 1) is noninvasive compared with other imaging modalities, 2) does not use radiation, and 3) does not require intravenous contrast, while at the same time it maintains high sensitivity for aneurysm detection.⁸ The use of MRA also simulates the clinical setting whereby it is the most likely radiological investigation offered as a screening tool for asymptomatic individuals.

CTA was used for confirmatory imaging following our institutional practice of confirming incidental MRA findings in asymptomatic patients. CTA is less invasive and is not associated with a risk of stroke as compared with the gold standard of digital subtraction angiography;^{6,16} both modalities are considered diagnostically equivalent. CTA is also more acceptable for asymptomatic patients with their natural inclination to not investigate further.

Moreover, the difference in measurements of aneurysm size between good quality 3D CTA and digital subtraction angiography is less than 1 mm.²⁰ Furthermore, 3D measurement of aneurysm size from CTA has high interobserver and intraobserver reliability.¹⁷

Results

There were 114 consecutive patients with SAH due to a ruptured aneurysm during the study period (Fig. 1). None of the screened patients had a first-degree relative with a history of aSAH. In total we identified 347 asymptomatic first-degree relatives. Three hundred five (87.9%) consented to participate and were successfully recruited to undergo MRA. Forty-two asymptomatic first-degree relatives (12.1%) did not participate. The reasons these 12.1% did not undergo MRA included refusal to consent, claustrophobia, presence of nail in the eye, presence of metallic

FIG. 1. Study participant flow diagram. Figure is available in color online only.

screws and implant in body parts, physically not in Hong Kong, or failed to attend the MRA appointment.

Of 305 MR angiograms performed, 248 (81.3%) were normal, and 57 (18.6%) were abnormal. Of the 57 abnormal MR angiograms, 23 (7.5%) showed suspected UIAs, and 34 (11.1%) had other findings including old infarction, vessel stenosis, small-vessel disease, old hemorrhage, and osteoma. Of the 23 MR angiograms with suspected UIAs, 20 proceeded with CTA and 3 did not. Reasons for not undergoing CTA included refusal to consent, diabetes and taking metformin, and physically not in Hong Kong. Of the 20 with suspected UIAs that proceeded with CTA, 7 confirmed the presence of a UIA (Table 1) and 13 showed no abnormality (Table 2). The prevalence rate of UIAs in this population of first-degree relatives was thus 2.30% (95% CI 1.02%–4.76%).

The sizes of the 7 UIAs detected ranged from 1.4 mm to 7.5 mm (Table 1). Six (85.7%) of the 7 UIAs were smaller than 5 mm (range 1.4 mm–3.1 mm). None of these 6 UIAs underwent an endovascular procedure or surgical intervention. The only UIA that was larger than 5 mm was a right intracranial vertebral artery (VA) saccular aneurysm in a 62-year-old woman. It measured 6.3 mm wide by 7.5 mm long. Stent placement using the Pipeline Embolization Device (ev3) was performed in September 2011. There had been no transient ischemic attack or stroke at the latest follow-up evaluation in October 2014. The latest CTA in October 2014 showed a patent right VA with no in-stent stenosis.

None of the UIAs identified ruptured or became symptomatic during the follow-up period, ranging from 31 to 55 months (median 43 months). Of the 3 suspected UIAs on MRA that did not undergo CTA, one was a 4.8 × 2.5-mm left internal carotid artery (ICA) aneurysm in a 46-year-old woman, one was a 2-mm left ICA aneurysm in a 44-year-old woman, and the third was a 2-mm anterior communicating artery (ACoA) aneurysm in a 48-year-old woman (Table 3).

To assess the impact of selection bias, for example, whether the prevalence could have been higher if the older population did not refuse MRA or CTA, we compared the age and sex ratios in the different groups. The ages of the 42 first-degree relatives who were identified and invited but did not undergo MRA ranged from 1 to 71 years old (mean 37.8 years old). After excluding those under the age of 21, the ages ranged from 21 to 71 years old (mean 47.8

TABLE 2. Findings in 13 patients who underwent MRA for suspected UIAs with normal CTA results

Age (yrs), Sex	MRA Findings
31, M	Lt PCoA aneurysm
39, M	Rt MCA aneurysm
45, M	Suspected ACoA aneurysm
47, M	Suspected rt PCoA aneurysm
49, F	Suspected rt PCoA aneurysm
51, F	Bilat PCoA aneurysm
53, M	Suspected rt ICA aneurysm
55, F	Aneurysm of the orbitofrontal branch of the lt ACA
55, F	Suspected lt PCoA aneurysm
60, F	Small aneurysm at origin of lt PCoA
62, M	Small aneurysm in the rt ICA
62, F	Small aneurysm in the lt ICA at the ophthalmic artery
64, M	Suspected lt PCoA aneurysm

MCA = middle cerebral artery; PCoA = posterior communicating artery.

years old). There were 24 males and 18 females (ratio: 1 to 0.75). The ages of the patients with 7 confirmed UIAs ranged from 25 to 62 years old (mean age 50.7 years old). There were 4 men and 3 women (ratio: 1 to 0.75). The ages of the 13 patients with suspected UIAs on MRA but normal CTA results ranged from 31 to 64 years old (mean 51.8 years old). There were 7 men and 6 women (ratio: 1 to 0.86).

Discussion

In this study, the prevalence of UIAs in asymptomatic Hong Kong Chinese with 1 first-degree relative with a positive history of aSAH was 2.30% (95% CI 1.02%–4.76%), which is lower than rates cited in the literature. A systematic review and meta-analysis of prevalence studies showed that the prevalence of UIA was 3.2% (95% CI 1.9%–5.2%) in a population without comorbidity. A prevalence ratio of 3.4 (95% CI 1.9–5.9) was found for a positive family history of intracranial aneurysm or SAH.¹³ One screening study showed that 4% (95% CI 2.6%–5.8%) of patients with aSAH had first-degree relatives with UIA.¹⁰

At the same time, the incidence of aSAH in Hong Kong has been reported to be 7.5 (range 6.9–8.2) per 100,000 person-years.¹⁸ This is comparable to the data cited in the literature, in which the incidence of aSAH has been estimated to be approximately 7.8 (95% CI 7.2–8.4) per 100,000 person-years in most populations.^{9,12,13} With the discrepancy in prevalence of UIAs, yet a similar incidence of aSAH, one probable explanation is that UIAs in Hong

TABLE 1. Computed tomography angiography findings in 7 patients with confirmed UIAs

Age (yrs), Sex	CTA Findings
25, M	2-mm rt ICA aneurysm
43, M	1.4-mm lt ICA aneurysm
49, F	2.5-mm lt ICA aneurysm
57, F	3.1-mm rt ICA aneurysm
58, M	2-mm rt ACA aneurysm
61, M	2-mm rt ICA aneurysm, 2.2-mm lt ICA aneurysm
62, F	7.5-mm rt VA aneurysm

ACA = anterior cerebral artery.

TABLE 3. Magnetic resonance angiography findings in 3 patients with suspected UIAs who did not undergo CTA

Age (yrs), Sex	MRA Findings
44, F	2-mm lt ICA aneurysm
46, F	4.8-mm lt ICA aneurysm
48, F	2-mm ACoA aneurysm

Kong Chinese ruptured at a smaller size. This coincides with our data that showed most of the UIAs identified were < 5 mm.

Most of the UIAs detected in our study were small, in which 6 of 7 were < 5 mm (85.7%). With assumptive analysis of the 3 participants with suspected UIAs on MRA who did not undergo CTA, 2 more may also have harbored a true UIA (both ICA aneurysms, which were 2 mm and 4.8 mm in size, respectively); therefore 8 (88.9%) of these 9 were < 5 mm. Both of these values were higher than the value of 66% from the meta-analysis.¹⁴ A previous study from our center had suggested that ruptured intracranial aneurysms are smaller in Asians.¹⁸ With a similar incidence of aSAH in Hong Kong (7.5 per 100,000 person-years) as compared with the data from the literature, the hypothesis that UIA rupture risk size threshold is different in Chinese should be further investigated.

Screening with either CTA or MRA is usually recommended for first-degree relatives of families with 2 or more members with aneurysms or aSAH.⁵ Moreover, a long-term serial screening study for UIAs in families with 2 or more aSAHs or UIAs showed a substantial yield of 3%–5% of newly identified UIAs after more than 10 years of follow-up and 2 initial negative screenings,³ supporting the rationale of offering screening in this population.

Currently, screening is not generally recommended if there is only 1 family member with an aneurysm or aSAH.¹ However, the latest data have suggested a strategy of screening once for UIA in persons with 1 first-degree family member with aSAH during that person's lifetime; screening at an age between 30 and 55 years was the most cost-effective with the lowest costs per quality-adjusted life years.²

At the same time, proper counseling is crucial in the process of offering screening. This is particularly important if the UIAs identified are small and do not undergo intervention, because the potential benefits of a positive result of screening could be offset by depression and a reduction in quality of life.¹⁵ This is consistent with the fact that none of the small UIAs (< 5 mm) identified in our study underwent intervention. This is justifiable because this strategy is balanced against the potential risks of intervention, be they endovascular coiling or clip placement.⁴

There were limitations in the current study. The number of first-degree relatives with UIAs was small. However, as the prevalence was approximately 2%, the overall UIAs yielded could have been increased by approximately 2 after screening of about another 100 asymptomatic persons using MRA, which was limited by funding and resources for our study. Of the eligible first-degree relatives, 12.1% did not undergo MRA for various reasons. No interobserver reliability was assessed. MRA was performed at the University Radiology Department's neuroradiology imaging session. The angiograms were read and reported by the consensus of 2 or 3 neuroradiologists, as is our usual standard of practice. The aim of the study was to generate data on the prevalence of UIAs, and interobserver reliability was thus not incorporated into the study design. The diagnostic yield might be different with a different MRI machine and protocol, which was not addressed in

the current study. Three first-degree relatives with MRA-detected UIAs did not undergo CTA. This group could have harbored UIAs. However, it was limited by subjects' refusal to consent, which in turn was an objective reflection of the practical difficulty in this clinical situation. There was no family with 2 or more first-degree relatives with a ruptured aneurysm and SAH during the study period. Thus, we cannot comment as to whether there was any yield in families with 2 or more first-degree relatives in our study. There was no family with more than 1 first-degree relative who screened positive for an unruptured aneurysm. Hence we are unable to investigate the rate of UIAs in those with a single affected family member versus those with more than 1 member.

Because of not only the relative low incidence of UIAs but also the fact that most of the aneurysms found were very small and probably do not need to be treated, we do not recommend the practice of general screening of first-degree relatives of patients with aSAH if there is no history of a second immediate member of the family having had an aneurysm. At the same time, we need to acknowledge the existing uncertainty on the natural history of UIAs.⁷

Conclusions

The prevalence of UIAs in first-degree relatives of patients with aSAH in Hong Kong Chinese in this study was 2.30% (95% CI 1.02%–4.76%), which is lower than that in Caucasians, while most of the UIAs detected in our study were small (85.7% were < 5 mm, vs 66% in a meta-analysis).

Acknowledgment

This study was supported by a direct grant for research from the Chinese University of Hong Kong (no. MD09731).

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Wong, Ahuja. Acquisition of data: Wong, Abrigo, Cheung, Siu, Ahuja. Analysis and interpretation of data: Wong, Chan, Siu. Drafting the article: Wong, Chan. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Wong. Statistical analysis: Wong, Chan. Administrative/technical/material support: all authors. Study supervision: Wong.

Supplemental Information

Previous Presentation

Part of the paper was previously presented as an oral presentation on November 2, 2013, at the Conjoined Congress of the 5th World Conference of Intracerebral Hemorrhage (ICH) & 20th Annual Scientific Meeting of the Hong Kong Neurosurgical Society, in Hong Kong.

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