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Clinical Article

The natural history of cerebral infundibula: A retrospective cohort study

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Objective: Debate exists regarding the true pathogenicity of cerebral infundibula (CI). Pre-aneurysmal lesions and benign anatomical variants have both been proposed. In this study, we present the largest single cohort series on the natural history of CI.

Methods: Retrospective review of prospective surveillance of 420 CI was undertaken in a single tertiary cerebrovascular centre. All CI diagnosed by a neuroradiologist, diagnosed on either a Magnetic resonance angiography (MRA), Computed tomography angiography (CTA) or Digital subtraction angiography (DSA) were eligible for inclusion. Imaging and demographic characteristics were recorded at baseline. CI growth and aneurysm transformation were the outcomes of interest. Groupwise comparison was conducted via Fischer exact testing. Kaplan Meir curves and Cox proportional hazard ratios were used to assess variables of interest with respect to time on surveillance.

Results: 402 patients with 420 CI were surveyed over 2418 infundibula-years. Eleven CI (2.62%) grew on surveillance, and three (0.7%) transformed into aneurysms. Median time to growth was 85 months (36-263) and median time to aneurysm transformation was 112 months (96-142). Of the CI that grew, male sex and CI >2 mm at diagnosis were significant predictors of growth (all $p<0.05$). Of the CI that grew in surveillance, 2/11 (18.2%) transformed into aneurysms ($p=0.001$). Aneurysm transformation occurred at a rate of 1.27 per 1000 infundibula years. CI growth on surveillance ($p=0.00016$) and size at diagnosis ($p=0.038$) remained significant predictors of aneurysm transformation on Kaplan Meir curves.

Conclusions: The transformation of a CI to an aneurysm occurs at a low rate. A history of growth on surveillance imaging represents significant risk for aneurysm transformation.

Keywords Neurosurgery, Intracranial aneurysm, Infundibulum, Disease progression

INTRODUCTION

A cerebral infundibulum (CI) is a dilatation of a cerebral vessel, described as being

funnel shaped and arising at the origin of a branching vessel. Histological evaluation of CI suggests they are distinct from aneurysms.[15] Definition of CI vary; however, they often include size limitations and preclusions to where the continuing vessel may arise from them.[4] Previous literature describes a prevalence of 7-25%.[8] Historically CI have been regarded as anatomical variants with minimal clinical significance. However, case reports of infundibular growth and rupture resulting in subarachnoid hemorrhage exist.[1)3)5)6)9)12)14)17)] This has led to some arguing that CI represent pre-aneurysmal lesions.[1)4)5)6)8)12)15)] An abundance of literature and guidelines are present with respect to the treatment and surveillance of patients with unruptured intracranial aneurysms.[2)10)11)18)]

There are no large or adequately powered cohort studies which examine the risk of infundibula growth or aneurysm formation. Subsequently, there is little literature to inform surveillance or treatment guidelines for CI. In this study, we aim to define the natural history of CI to determine whether they are a benign entity or whether surveillance is required to assess for growth or aneurysm transformation. Further, we aim to examine risk factors for growth and aneurysm transformation to inform surveillance paradigms. To our knowledge, this represents the largest observational study in literature regarding the natural history of infundibula.

MATERIALS AND METHODS

Database formulation and demographics

The patient population for this study was derived from an electronic database consisting of sequential presentations to a tertiary neurosurgical centre between 2000 and 2021. Cerebral infundibula in this database were either under prospective surveillance due to the patient having other cerebral aneurysm warranting surveillance, or they were patients with isolated cerebral infundibula which were under surveillance. Prospective surveillance of isolated infundibula was departmental policy during the study period due to perceived risk of aneurysm transformation. Surveillance consisted of yearly computed tomography angiogram (CTA) or magnetic resonance angiogram (MRA) for at least the first 5 years; thereafter, follow-up intervals varied (median follow-up 60 months, range 14 to 263 months). Demographic and clinical variables, including age, sex and medical co-morbidities were entered into the database at baseline. In total, we retrieved 402 patients with 420 cerebral infundibula. This study was approved by the local ethics committee.

Definition of an infundibular dilatation

The diagnosis of cerebral infundibula was made using either digital subtraction angiography (DSA), MRA or CTA in all cases. Diagnosis was made in all cases by an expert neuroradiologist. All infundibula diagnosis were retrospectively verified prior to inclusion in this study.

The radiographic inclusion criteria for the diagnosis of CI in this study were as follows:

1. There were no restrictions on arterial location.
2. The lesion had to be funnel shaped, with a base larger than its apex.
3. The cerebral infundibula had to be located at the origin of the branching vessel.
4. The branching vessel had to continue from the apex of the cerebral infundibula.
5. No irregularities to the lesion

Some authors define these lesions as having an ostium less than 3 mm in diameter, we included lesions with an ostium wider than 3 mm in this study.[4]

Thirteen patients (n=13) that were initially entered into the database and were subsequently excluded based on retrospective review radiographic criteria. These lesions had the following exclusion criteria.

1. More than one branching vessel from the apex.
2. The branching vessel arose from the wall lesion before the apex.
3. Irregularities in shape or were not funnel shaped.

Radiographic variables and outcomes

All patients had imaging available electronically and

measurements were made using the hospital digital imaging system. The maximum size, height, and neck width were measured on a 0.1 mm scale in line with what has been reported elsewhere.[4] Radiographic outcomes of interest were infundibula growth and aneurysm transformation. Growth was defined as an increase in size of 1 mm compared to the index scan. Denovo aneurysm formation from an infundibulum was defined as radiographic features more in keeping with an aneurysm. In all cases, this was loss of its funnel shape. (Fig. 1)

Statistical analysis

All statistical analysis was performed in R.[13] Categorical data was expressed as frequency and percentages. Continuous data was examined for normality, via Shapiro–Wilk normality test.[16] Data was subsequently expressed as median and range for nonparametric data and mean and standard deviation for parametric data. Non-parametric testing was by means of Mann-Whitney U test, whilst parametric analysis was via t-tests. Categorical data was compared via Fischer exact testing. For all data analysis a significance value of 0.05 was set.

To build regression models that predicted growth and aneurysm formation, all demographic, clinical and radiographic variables were tested via univariate Cox proportional hazards regression to assess relationships to both outcomes of interest.[7] Variables with a p value of <0.1 were considered for multivariate regression. Variable independence was verified using Spearman's correlation co-efficient prior to multivariate regression modelling. A forward stepwise multivariate Cox proportional hazard regression model was then performed in order of the magnitude beta coefficients. Variables were added until all significant variables were used, or the model became non-significantly different in prediction when the additional variable was added. Subsequent hazard ratios were derived from regression modelling.

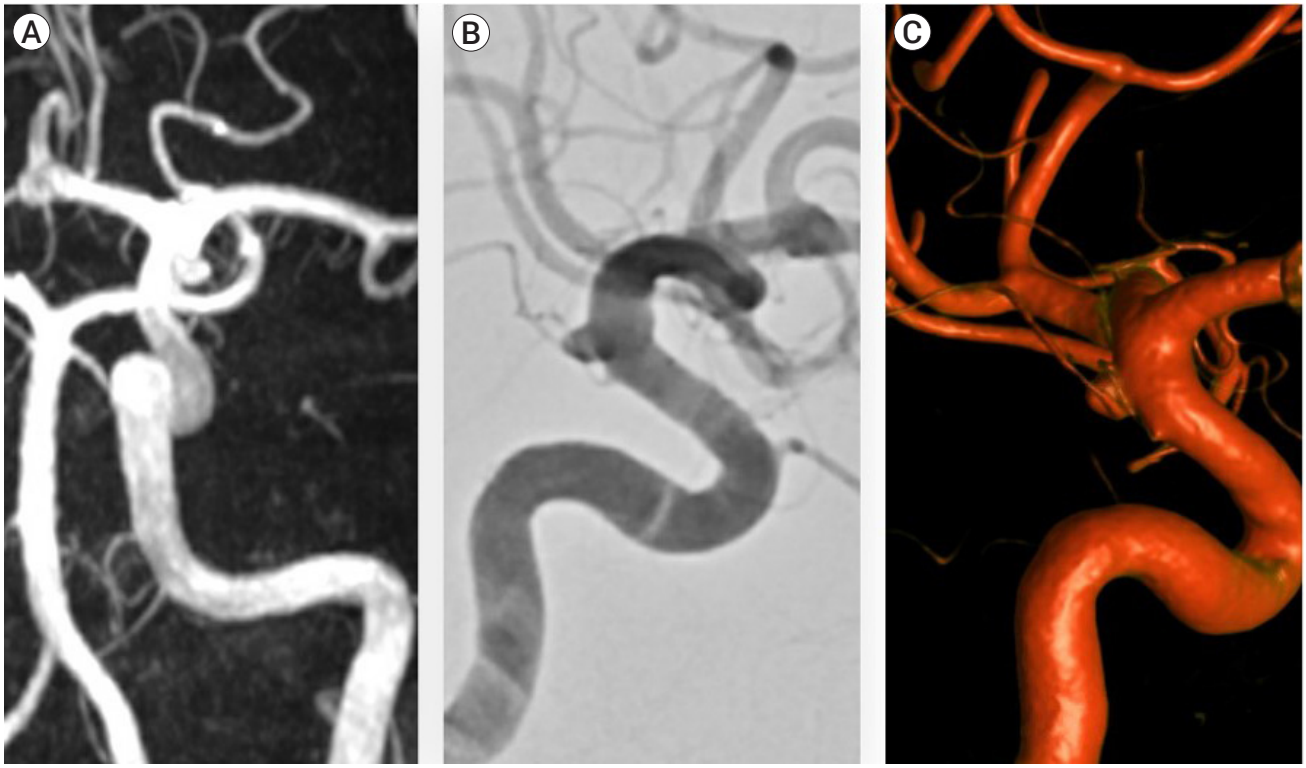

Fig. 1. (A–C) Sequential angiographic images of an internal carotid artery infundibulum which demonstrated growth and aneurysm transformation over a 5-year observation period

RESULTS

Patient population

In total 402 individual patients, incorporating 420 CI were analysed. Sixteen patients had two CI, and a single patient had three (Table 1). 35.95% (n=124) were diagnosed on DSA, 34.29% (n= 150) were diagnosed on computed tomography angiography (CTA) and 29.74% (n= 143) were diagnosed on magnetic resonance angiography (MRA). Posterior communicating artery (PCOM) represented the most common arterial location of the CI, accounting for 49.05% (n= 206). Other cerebral aneurysms were present in 58.5% (n= 235) of patients. In total, 11 CI (2.64%) grew during follow-up. This gave a rate of growth of 4.66 per 1,000 infundibula-years. Three patients (0.71%) developed aneurysms from infundibula on prospective surveillance. This gave a rate of aneurysm development of 1.27 per 1,000 infundibula years.

The posterior communicating artery represented the most common location of CI, accounting for 49% (n= 206/420) of total CI in the study. The distribution of CI with respect to artery location was statistically significantly different than would be expected by chance alone

Table 1. Patient demographics

Patient characteristics	N= 402	
Demographics	Count	%
Sex		
Male	285	70.9%
Female	113	28.1%
Unknown	3	1%
Age at diagnosis	55.85 ± 12.54	
Duration of follow-up (months)	69.27 ± 38.81	
Number of infundibula	420	
Infundibulum per patient	Count	%
Singular	385	95.7%
Two	16	4.0%
Three	1	0.2%
Diagnosis means	Count	%
DSA	124	36.0%
MRA	143	29.7%
CTA	150	34.3%
ARTERY TERRITORY	Count	%
ACA	10	2.4%
ACOM	10	2.4%
AICA	2	0.5%
ANTERIOR CHOROIDAL	30	7.1%
BASILAR	7	1.7%
ICA TERMINUS	96	22.9%
MCA	25	6.0%
OPHTHALMIC	10	2.4%
ORBITOFRONTAL	1	0.2%
PCA	12	2.9%
PCOM	206	49.1%
PICA	2	0.5%
SCA	7	1.7%
VERTEBRAL	2	0.5%
Growth on surveillance	11	2.64%
Size of infundibulum		
>3 mm	50	11.9%
<3 mm	352	88.1%
Vascular history		
Previous history of subarachnoid haemorrhage		
Yes	263	65.4%
No	145	36.1%
Uncertain	4	1.0%
Hypertension history		
Yes	215	53.5%
No	147	36.6%
Uncertain	40	9.9%
Smoking status		
Ex-Smoker	7	1.7%
Current	211	52.5%
Nonsmoker	131	32.6%
Uncertain	53	13.2%
Family history of subarachnoid haemorrhage		
Prior family history	20	5.0%
No family history	202	50.3%
Uncertain	180	44.8%
Other cerebral aneurysm present		
Yes	235	58.5%
No	167	41.5%

DSA, digital subtraction angiography; MRA, magnetic resonance angiography; CTA, computed tomography angiography

(p<0.001). ICA terminus was included as a location when it was unclear the exact named branching vessel and thus location may be understated (Table 2).

Out of the 11 CI that grew the most common location was the terminus of the Internal carotid artery (n=5/11; 45.5%). Although, amongst the CI that grew, no one artery was overrepresented than would be expected by chance alone (p=0.21). Arterial location groupings with respect to traditional aneurysm risk stratification tools, including PHASES 2 and ISUIA 10 provided some predictive value on the univariate Cox hazard regression modelling. Specifically, 'Posterior circulation' of ISUIA (HR: 0.22, 95% CI 0.06, 0.86; p=0.029) and 'other' grouping on PHASES (HR: 0.22, 0.06, 0.87; p= 0.032) demonstrated protective effects on CI growth (Table 3).

There was a preponderance for growing infundibula to be diagnosed on imaging modalities other than DSA (10/11 vs 1/11; p= 0.006). For these lesions, DSA was often used to confirm diagnosis. Though, the means of imaging modality did not directly predict growth (Table 4).

On univariate regression analysis size grouping (<2 mm vs 2-3 mm vs >3 mm), male sex and posterior circulation per ISUIA and 'other' per PHASES, yielded statistically significant predictors of CI growth. Initial diagnosis on DSA yielded near significant prediction (p=0.064). In multivariate modelling, size grouping and male sex remained statistically significant predictors. Kaplan Meir graphs are presented in Fig. 2.

Time to growth and size at diagnosis were independent of each other (r=0.04; p >0.05). The risk factors for CI growth combined are displayed in the below table. In the presence of lowest combination risk factors (ie female sex and <2 mm), CI followed for 10 years or more, grew at a rate of 1 in 33. At 10 years of follow-up, this gave a sensitivity of 88.9% (95% CI 51.75% to 99.72%) and specificity of 4.17% (0.11% to 21.12%) in predicting CI growth. Notably, 7 of the 11 CI grew after 5 years follow-up. Risk of CI growth was equal over the entire study duration, except in CI surveyed for 138 months or more. The odds of growth in those surveyed for 138 months or more was 5.51 (95% CI: 1.094-27.759; p= 0.019), compared to those surveyed less (Table 5).

Three CI transformed into aneurysms on surveillance. Aneurysm transformation occurred at a median follow-up of 112 Months (range: 96-142). All aneurysms showed a history of growth on surveillance, and all were >2 mm at diagnosis. In univariate Kaplan Meir analysis,

Table 2. Distribution on infundibula

CI growth status	Count	Percent
Increased	11	2.62%
ACOM	1	9.09%
BASILAR	1	9.09%
ICA TERMINUS	5	45.45%
MCA	1	9.09%
PCOM	3	27.27%
Stable	406	96.67%
ACA	10	2.46%
ACOM	9	2.22%
AICA	2	0.49%
ANTERIOR CHOROIDAL	30	7.39%
BASILAR	6	1.48%
ICA TERMINUS	91	22.41%
MCA	24	5.91%
OPTHALMIC	10	2.46%
ORBITOFRONTAL	1	0.25%
PCA	12	2.96%
PCOM	200	49.26%
PICA	2	0.49%
SCA	7	1.72%
VERTEBRAL	2	0.49%
Uncertain	3	0.71%
PCOM	3	100.00%

CI, cerebral infundibula; ACOM, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCOM, posterior communicating artery; ACA, anterior cerebral artery; AICA, anterior inferior cerebellar artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; SCA, superior cerebellar artery

Table 3. Infundibula diagnosis modality by change in size

Row labels	Increased	Stable	Grand total
CTA	6	141	147
DSA	1	123	124
MRA	4	139	143
Grand total	11	403	414

CTA, computed tomography angiography; DSA, digital subtraction angiography; MRA, magnetic resonance angiography

Table 4. Univariate Cox hazard regression analysis for infundibula growth

Characteristic	N	HR	95% CI	p- value
Demographics				
Age at diagnosis	407	1.02	0.96, 1.07	0.6
Sex	418			
Female		—	—	
Male		4.84	1.36, 17.3	0.015
Imaging modality	420			
CTA		—	—	
MRA		0.45	0.11, 1.82	0.3
DSA		0.13	0.02, 1.12	0.064
Artery characteristics				
Size of infundibula	420			
<2 mm		—	—	
2-3 mm		13.4	1.64, 109	0.015
>3 mm		19.7	1.78, 218	0.015
IUSIA grouping	420			
Anterior circulation				
Cavernous		NC		>0.9
Posterior circulation		0.22	0.06, 0.86	0.029
PHASES grouping	420			
ICA				
MCA		0.67	0.07, 6.06	0.7
Other		0.22	0.06, 0.87	0.032
Multiple infundibula present	420	1.03	0.13, 8.36	>0.9
Vascular risk factors				
Smoker	364			
No		—	—	
Yes		NC		>0.9
Family history of subarachnoid Haemorrhage	419			
No		—	—	
Yes		NC		>0.9
Other aneurysm present on imaging	420			
No		—	—	
Yes		0.71	0.20, 2.50	0.6
Hypertension	378			
No		—	—	
Yes		0.55	0.14, 2.22	0.4
Antiplatelets	372			
No		—	—	
Yes		0.47	0.06, 3.79	0.5
Previous subarachnoid haemorrhage History	416			
No		—	—	
Yes		1.84	0.53, 6.38	0.3

HR, hazard ratio; N, number; 95% CI, 95% confidence interval; CTA, computed tomography angiogram; MRA, magnetic resonance angiogram; DSA: digital subtraction angiography

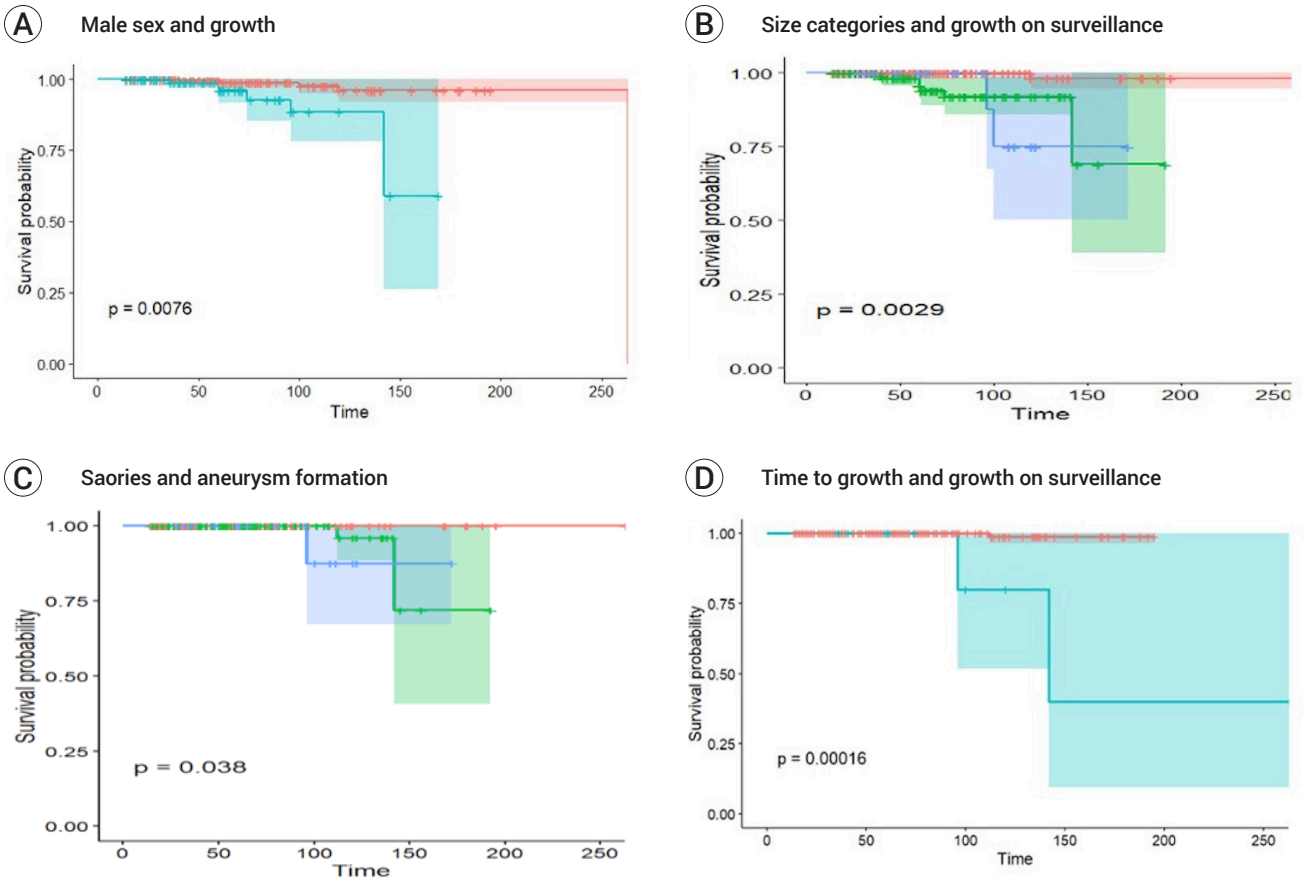

Fig. 2. Kaplan Meier curves for outcomes of interest (A) Kaplan Meier Curve for time to growth for male sex as the variable (Blue: male sex, Red: female sex). (B) Kaplan Meier curve for time to growth for size groupings as the variable (Red: <2 mm in size); Blue: 2-3 mm in size, Green >3 mm in size. (C) Kaplan Meier Curve for time to aneurysm transformation for size groupings as the variable (Red <2 mm in size; Blue: 2-3 mm in size, Green >3 mm in size). (D) Kaplan Meier Curve for time to aneurysm transformation for growth on surveillance as the variable (Red: no growth; Blue: growth on surveillance)

Table 5. Multivariate Cox hazard regression model in predicting infundibula growth

Characteristic	HR	95% CI	p-value
Male sex	4.35	1.18, 16.0	0.027
Size grouping			
<2 mm	—	—	
2-3 mm	11.2	1.37, 92.0	0.024
>3 mm	22.0	1.97, 246	0.012

HR, hazard ratio; 95% CI, 95% confidence interval

both growth on surveillance and size grouping predicted aneurysm formation predicted aneurysm formation. The hazard ratios for growth on surveillance was 87.8 (95% CI 7.75, 1,995; p<0.001). Given no aneurysms formed in the reference size group (<2 mm), infinite estimates prevented calculation of hazard ratio with respect to size grouping.

DISCUSSION

Multiple guidelines and decision making tools exist for the assessment and management of intracranial aneurysms, however, none exist for CI. We analysed 420 CI for radiological growth, rupture and aneurysm transformation for over one decade. This is the largest natural history study of CI. We derived several important conclusions regarding the natural history of infundibula from this study. (Box 1)

- CI represent a benign entity in most, progression to aneurysm occurs at 1.27 per 1,000 infundibula years.
- Growth and aneurysm transformation occur after prolonged periods of time (>5 years).
- CI size predicts growth and aneurysm formation, but no absolute size cutoff exists with

Box 1: Seminal study findings

Overall, the absolute risk of CI growth on surveillance in our population was 2.6%. CI growth occurred at a rate 4.66 per 1,000 infundibula years. However, CI growth was difficult to predict. Growth is probably a random event, however, it has been believed that hemodynamic factor plays a major role contributing to the progression of an infundibulum to true aneurysm such as a well-developed posterior communicating artery (fetal type P-com).4 In this study, of the 206, PCOM infundibula, 111 had a fetal type PCOM and of the 11 CIs which grew during follow-up, only 3 P-coms (3/11, 27.27%) were included, however, there was no fetal type P-com. This was asserted by the lack of relationship between CI size and time to growth (r=0.04; p>0.05). CI which was >2 mm at diagnosis was more likely to grow (HR: 11.2; 95% CI: 1.37-92.0; p=0.024). Similarly, male patients were also more likely to have CI that grew (HR= 4.35; 95% CI: 1.18-16.0; p=0.027). No other features were associated with growth. Despite being able to elicit the risk factors for growth of CI on surveillance, when combined, these risk factors yielded a predictive sensitivity which was suboptimal for clinical use (Sensitivity=88.9%; 95% CI 51.75% to 99.72%) (Table 6). The longest period of time to growth occurred at 263 months. Many of the CI showed growth late during their follow-up (7/11, after 5 years). This would suggest that growth occurs after a prolonged period on surveillance (Table 7).

Three (0.7%) of the four hundred and twenty infundibula transformed into aneurysms during their surveillance. Transformation to an aneurysm occurred at a rate of 1.27 per 1,000 infundibula years. Overall, this represents a rare occurrence. In all cases, aneurysm diagnosis was made after 5 years of radiological surveillance. Risk factors for this were growth on surveillance imaging (HR: 87.8; 95% CI 7.75-1,995; p<0.001) and larger size at diagnosis (p=0.038). In the absence of both risk factors, no CI progressed to aneurysm formation. Therefore, growth of a CI on sequential imaging probably represents a lesion that is "pre-aneurysmal" as opposed to a CI.

There are several limitations to this study. Firstly, this study was a single centre cohort which may limit the generalisability of these findings. A multicentre study is ultimately required to validate the findings of this study. There is also a probable selection bias inherent in the setting of this study. There may have been incidental CI not referred to our centre during the study period. Risk of growth and aneurysm transformation

Table 6. Growth of CI at follow-up periods and risk factors

	Total		3 years		5 years		10 years	
	Stable	Growth	Stable	Growth	Stable	Growth	Stable	Growth
Female	279	5	219	0	139	1	21	4
<2 mm	182	2	140	0	86	0	1	1
2-3 mm	84	2	68	0	44	1	8	2
>3 mm	13	1	11	0	9	0	2	1
Male	109	6	85	0	41	3	3	5
<2 mm	70	0	47	1	19	0	1	0
2-3 mm	34	5	33	0	18	3	2	4
>3 mm	5	1	3	1	4	0	0	1
Total	388	11	303	1	180	4	24	9

Table 7. Univariate Cox hazard regression analysis for aneurysm formation

Characteristic	N	HR	95% CI	p-value
Demographics				
Age at diagnosis	407	1.02	0.92, 1.13	0.7
Sex	418			
Female		—	—	
Male		7.11	0.64, 78.7	0.11
Imaging modality	420			
CTA		—	—	
MRA		1.58	0.14, 17.4	0.7
DSA		NC		
Artery characteristics	420			
Size >3 mm at diagnosis	420			
Multiple infundibula present	420		NC	
Growth on surveillance	420	31.8	2.57, 394	<0.001
Size of infundibula	420			
<2 mm		—	—	
2-3 mm			NC	0.99
>3 mm			NC	0.99
IUSIA grouping	420			
Anterior circulation		—	—	
Cavernous		1.17	0.11-25.2	0.99
Posterior circulation			NC	0.99
PHASES grouping	420			
ICA		—	—	
MCA			NC	0.99
Other		0.65	0.06-14.0	0.7
Vascular risk factors				
Smoker	364			
No		—	—	
Yes		3.92	NC	>0.9
Family history of Subarachnoid haemorrhage	419			
No		—	—	
Yes			NC	>0.9
Other intracranial aneurysm on imaging	420			
No		—	—	
Yes		1.10	0.09, 13.3	>0.9
Hypertension	378			
No		—	—	
Yes			NC	
Antiplatelets	372			
No		—	—	
Yes		2.12	0.19, 23.3	0.5
Previous history of Subarachnoid haemorrhage	416			
No		—	—	
Yes			NC	>0.9

95% CI, 95% confidence interval; CTA, computed tomography angiogram; MRA, magnetic resonance angiogram; DSA, digital subtraction angiography

may therefore be overstated in this study as no CI came to attention due to rupture in this study. Naturally, intra and inter-observer bias is present when reporting small changes within lesions or even when defining a vascular dilatation as an infundibulum or an aneurysm. Another limitation of the paper is the use of CTA and MRA for surveillance of infundibula, as many clinicians believe that DSA is necessary, however in our study, DSA was used to confirm diagnosis and given the additional invasive risks of cerebral angiography, not routinely used to monitor seemingly low risk lesions. Overall, further prospective multicentre studies with strict radiographic CI diagnosis criteria are required to validate these findings reported in this study.

CONCLUSIONS

In conclusion, CI grow and transform into aneurysms; although, this is a rare event. Size of the CI and male sex predict CI growth, though do so imperfectly. If growth occurs, it often occurs after prolonged periods of follow-up. CI that show growth on interval imaging likely represent a "pre-aneurysmal" lesion and not a CI. Future multicentre large prospective cohorts are required to confirm the findings of this study.

Disclosure

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

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