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ORIGINAL RESEARCH

Results of Screening for Intracranial Aneurysms in Patients with Coarctation of the Aorta

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BACKGROUND AND PURPOSE: IAs are found in 2.3% of adults; the mean age at detection is 52 years. Prevalence is <0.5% in young adults. Early studies suggest that 10%–50% of patients with aortic coarctation have IAs. Screening recommendations are variable. We sought to examine the prevalence of IAs through screening with MRA.

MATERIALS AND METHODS: Consecutive patients older than 16 years of age with coarctation undergoing brain MRA between May 1999 and October 2007 were included. MRA was performed by using a 1.5T scanner with a 3D time-of-flight protocol; simultaneous MR imaging was performed of the heart and aorta. Cerebral MRAs were double-reported by a neuroradiologist. Statistics are described as mean ± SD and median ± range. Continuous variables were compared by using Student *t* tests and Mann-Whitney *U* tests (categoric variables, by using the Fisher exact test).

RESULTS: One hundred seventeen MRAs were double-reported. The median age was 29 ± 11 years (range, 16–59 years). IAs were found in 12 patients (10.3%). The mean diameter of IAs was 3.9 mm (range, 2.0–8.0 mm). Patients with aneurysms were older (median, 37 years; range, 16–50 years) than those without (median, 23 years; range, 16–59 years; $Z = -2.01$, $P = .04$). Hypertension was more common in those with IAs (IA 83% versus no IA 43%, $P = .01$). There was no association between ascending aortopathy, bicuspid aortic valves, and IAs.

CONCLUSIONS: Patients with coarctation have a higher prevalence of IAs, occurring at an earlier age than in population studies. Whether routine screening is appropriate for this group of patients is unclear. Hypertension is likely to be an important pathophysiologic factor.

ABBREVIATIONS AHA = American Heart Association; BHS = British Hypertension Society; IA = intracranial aneurysm

IAs are found in approximately 2.3% of adults (0.4%–6.0% in postmortem and angiography studies, respectively).[1,2] Studies by using brain MRA have suggested rates ranging between 0.1% and 1.8%, with very low rates for young adults.[3-5] IA rupture is the most common cause of nontraumatic SAH and, though uncommon,[6] is fatal within 30 days in almost half of patients.[1]

IAs have been described as being more common in patients with coarctation of the aorta. Older studies have suggested an IA prevalence of up to 50% in patients with coarctation,[7-9] and in 10% of those screened by MRA.[10] IAs have also been described as being prevalent in patients with bicuspid aortic valves, which commonly coexist with aortic coarctation.[11]

Hemorrhagic stroke has long been described as a cause of death in patients with coarctation of the aorta, accounting for approximately 5% deaths in the early surgical era.[8,12] However, recent large studies of IAs have not found aortic coarctation to be an independent risk factor for their rupture.[1,2,13,14]

Screening recommendations for detecting IAs in patients with aortic coarctation are variable. Recent guidelines from the AHA and American College of Cardiology for the management of patients with congenital heart disease in adulthood[15] do not mention IAs in patients with coarctation. The 2010 European Society of Cardiology guidelines suggest that "attention is required" for IAs but note that most clinicians see no indication for routine screening in asymptomatic patients.[16] The AHA guidelines for the management of patients with unruptured IAs do not recommend routine screening for asymptomatic low-risk patients.[17]

In our center, it has been standard practice to screen for IA once in all patients with coarctation at the time of first performing MR imaging of their aorta after the age of 16 years. All patients with coarctation of the aorta in our region undergo routine MR imaging of their hearts every 3–5 years in our center. IAs are referred for a neurosurgical opinion.

We retrospectively studied screening MRAs in a cohort of patients with coarctation to determine the prevalence of IAs and the relationship between clinical factors, such as aortopathy and hypertension, and IAs in coarctation of the aorta.

Materials and Methods

Data collection was approved by the University Hospitals Bristol Audit Committee.

Consecutive patients older than 16 years of age with aortic coarctation undergoing MRA of the intracranial arteries at the time of aortic scanning between May 1999 and October 2007 were included. There were no exclusion criteria. Baseline clinical data were collected from patients' notes on age; sex; previous coarctation surgery; smoking history; a documented diagnosis of hypertension in the clinical notes; bicuspid aortic valve, other congenital lesions; aortopathy or aneurysm at the site of coarctation or repair, as seen on MR imaging; drug therapy; and office systolic and diastolic blood pressure. Hyper-

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tension based on office blood pressure measurement was defined according to BHS guidelines[18] (grade 1, 140–159/90–99 mm Hg; grade 2, 160–179/100–109 mm Hg; grade 3, ≥180/110 mm Hg).

MRA of the intracranial arteries was performed by using a Symphony 1.5T scanner (Siemens, Erlangen, Germany) (with a dedicated head coil) by using 3D time-of-flight MRA protocol parameters: FOV, 200 mm; FOV phase, 75; section thickness, 0.83 mm; base resolution, 384 pixels; phase resolution, 70%; section resolution, 67%; voxel size = 0.7 × 0.5 × 0.8 mm; TR, 38 ms; TE, 5.28 ms; flip angle, 25°. Source data were reviewed in 3 orthogonal and oblique planes. Postprocessing maximum intensity projection images were generated to allow multiplanar reformatting. Scans were routinely reported by a cardiac radiologist and, for the purposes of this study, were subsequently independently reported by a separate neuroradiologist. The neuroradiologist was blinded to the initial report in most cases. The neuroradiological opinion was considered the criterion standard, and any new aneurysms discovered after the second reporting were addressed clinically. IAs seen were described in terms of site and size in millimeters.

Statistics are described as mean ± SD for parametric data (median ± range for nonparametric data). Continuous variables were compared by using the Student *t* test for parametric data (Mann-Whitney *U* test for nonparametric data). Categoric variables were compared by using the Fisher exact test. Correlation was done by a Spearman rank correlation.

Results

One hundred twenty-two scans were obtained in 122 patients. Five scans could not be retrieved for double-reporting. Therefore 117 scans were studied.

Median age of the patients was 29 years (range, 16–59 years); 46 were women. Baseline data can be found in Table 1.

IAs were found in 12 patients (10.3%); 8 were male (67%). The proportion of aneurysms observed in this cohort was significantly more than that expected in the general population, on the basis of a prevalence of 2% ($Z = 6.41$; 95% confidence interval, 4.8%–15.8%; $P < .0001$). The mean diameter of the aneurysms was 4.0 mm (range, 2.0–8.0 mm). Of these 12 aneurysms, only 3 were detected by non-neuroradiologists. Details of the aneurysms can be found in Table 2.

Both patients with aneurysms ≥5 mm were referred for neurosurgical opinion. One had elective endovascular repair of an 8-mm basilar termination aneurysm. Both continue to be monitored by annual MRA and neurosurgical review.

Size of the aneurysm was significantly correlated with the age of the patient ($r = 0.73$, $P = .010$).

The patients with IAs were compared with those without (Table 3). The patients with aneurysms (IA) were significantly older than those without (no IA): median, 37; range, 16–50 years (IA); median, 23; range, 16–59 years (no IA); $Z = -2.01$; $P = .04$.

A diagnosis of hypertension was prevalent, affecting almost half of patients (53 patients, 45%). A diagnosis of hypertension was significantly more common in the IA group, affecting 10 of 12 (83%) patients, compared with 43 patients in the no IA group (43%) ($P = .01$).

When measured office blood pressure was used in the analysis, there was no significant difference between the groups for either systolic (IA, 138 ± 12 mm Hg; no IA, 133 ± 17 mm Hg; $t = -0.95$; $P = .34$) or diastolic blood pressure (IA, 78 ± 10 mm Hg; no IA, 74 ± 12 mm Hg; $t = -1.24$; $P = .22$).

Of note, 29 patients fulfilled the BHS criteria for hypertension on the basis of their clinic blood pressure measurements (see above) (25 mild, 3 moderate, and 1 severe), but they were

Table 1: Baseline characteristics

Characteristic	No.
Sex	
Male	71
Female	46
Pre-existing hypertension	
Yes	53
No	60
Unknown	4
SBP	133 ± 16
DBP	73 ± 12
Smoker	
Yes	19
No	91
Unknown	7
Type of coarctation	
Native	10
Recoarctation	107
Aortic aneurysm	
Yes	12
No	105
Degree of recoarctation on MRI (of 107 repaired coarctations)	
None	50
Mild	33
Moderate	14
Severe	3
Not specified	7
Intracranial aneurysm on MRA	
Yes	12
No	105
Additional primary diagnosis	
BAV (± disease of subvalvar area)	47
Ventricular septal defect	10
Mitral valve abnormality	3
Supra-aortic stenosis	1
Patent arterial duct	2
Pulmonary stenosis	1
Anomalous pulmonary venous drainage	1
Single ventricle	1
Transposition of great arteries	2
No other lesion	46

Note:—BAV indicates bicuspid aortic valve; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2: Details of aneurysms and patient demographics

Site of Aneurysm	Size of Aneurysm (mm)	Sex	Age (yr)
Right MCA	4	F	38
Right PcomA	4	F	29
Right SCA	4	M	18
Left MCA	5	F	40
Left ACA	4	M	47
Right SCA	2	M	16
Left PcomA	4	M	41
Left MCA trunk	3	M	22
Left MCA trunk	3	M	24
Basilar termination	8	F	50
Right ICA bifurcation	3	M	35

Note:—PcomA indicates posterior communicating artery; SCA, superior cerebellar artery; ACA, anterior cerebral artery.

Table 3: Comparison of the aneurysm and no aneurysm groups

	Aneurysm (n = 12)	No Aneurysm (n = 105)	P Value
Age (yr)[a]	37 (16–50)	23 (16–59)	.04
Hypertension	83%	43%	.01
Smoker	25%	16%	.43
BAV or ascending aortopathy	42%	58%	.36
Aortic aneurysm	17%	10%	.36
SBP (mm Hg)[a]	138 ± 12	133 ± 17	.34
DBP (mm Hg)[a]	78 ± 10	74 ± 10	.22

Note:—BAV indicates bicuspid aortic valve; SBP, systolic blood pressure DBP, diastolic blood pressure.
[a] Data are median and range.

not receiving treatment or diagnosed as hypertensive. If those criteria were used for the definition of hypertension, there were still more patients with hypertension in the aneurysm group (IA, 10/12, 83%; no IA, 72/105, 51%; $P = .06$). A higher proportion of patients in the aneurysm group were smokers, but this was not statistically significant (IA, 25%; no IA, 16%; $P = .43$). More patients in the IA group had aortic aneurysms at the site of their coarctation or repair, as seen on MR imaging, but this was not statistically significant (IA, 17%; no IA, 10%; $P = .36$). Most interesting, there were fewer patients with IAs who also had a bicuspid aortic valve or ascending aortopathy than in the group with no IAs (IA, 42%; no IA, 58%; $P = .36$). The difference was not significant.

Discussion

Prevalence and Age

Several studies have specifically looked at the prevalence of IAs in young adults by using MRA and with neuroradiologic input. Katzman et al[19] found a prevalence of IA of 0.1% in 1000 healthy subjects with a median age of 29 years who underwent brain MRA. Weber and Knopf[20] found no aneurysms present in an MRA study of 2536 healthy men with a mean age of 20.5 years. However, in our study, 10.3% of patients were found to have an IA. Similar rates of IA in coarctation of the aorta have been reported elsewhere,[10] suggesting that IAs have a much higher prevalence (×100) in patients with coarctation of the aorta.

Our study confirms that patients with IAs and aortic coarctation tend to be younger than those with IAs and no coarctation.[10,21] In our study, the median age of patients with IAs was only 29 years (range, 16–59 years). Patients with IAs were, on average, 14 years older than those without, and the size of the aneurysm was significantly correlated with age. In the noncoarctation population, SAH caused by cerebral aneurysm rupture occurs at a mean age of 52 years,[1,2] but we do not know if IAs increase in size with age. The only patient we have seen in our service with coarctation who had a ruptured IA had previously undiagnosed coarctation, and her IA was not, therefore, picked up by screening. Two-thirds of those affected were men, in keeping with previous studies in younger patients.[10,22]

Cardiac Radiologist versus Neuroradiologist

In this study, the detection of IAs by cardiac radiologists was only 2.5%. Thus 9 (75%) aneurysms were missed when reported by specialist cardiac radiologists as opposed to neuroradiologists. Furthermore, the origin of the posterior inferior cerebellar artery was not routinely scanned in our MRAs. Up to 5% of aneurysms occur here, so theoretically more IAs may have been present.[23] We know that neuroradiologists perform better in detecting small IAs,[24] so this outcome begs the question of whether all scans should be reported by neuroradiologists. However, the only aneurysms missed by the cardiac radiologists were ≤4 mm, which are at a low risk of rupture. The double reporting of MRA by neuroradiologists would have a significant cost implication but may not have any practical clinical benefit. Our cardiac radiologists have now received informal training on reporting these scans, and in cases in which there is doubt about the existence of an aneurysm, a neuroradiology opinion is sought.

Size and Risk of Rupture

Although IAs were prevalent in our cohort, most were small and at low risk of rupture. The mean diameter of our aneurysms was 4.0 mm and very similar to that found in the Mayo Clinic cohort (mean diameter, 3.5 mm; identical range, 2.0–8.0 mm).[10] Most interesting, none of our patients had multiple aneurysms, in contrast to previous studies in which these have occurred in ≤14% of patients.[10,21] This may be due to the young age of the patients.

The question of what to do with tiny aneurysms found early in life is unanswered. With regard to aneurysm rupture, size is important. Those <10 mm have an annual rupture rate of as low as 0.05%; the rate is ≤1.9% for all aneurysms. According to the second publication of the International Study of Unruptured Intracranial Aneurysms, aneurysms of <7 mm in patients who had not had a previous SAH had a 0% per annum risk of rupture during 5 years in the anterior circulation and 0.5% in the posterior circulation.[25] IAs may remain completely stable, but they can also be prone to spurts of growth.[26]

Screening

The question of whether screening ought to be recommended is not straightforward. For any screening program to be successful, there has to be a serious disease with a predictable course, an asymptomatic phase, a useful test to detect the prodrome, and a safe treatment.

There is evidence that aneurysms may appear and rupture very quickly[27] and will be missed by screening. MRA is certainly a good screening test, being noninvasive, 81%–95% sensitive, and 80%–100% specific for the detection of IAs,[27] but the treatment of an asymptomatic IA carries significant risks. Elective endovascular repair has a morbidity/mortality rate of 3%–5%,[28] and this risk will outweigh the risk of rupture in many patients with small aneurysms. Whether the risks are justified in younger patients who may be exposed to an increased lifetime risk of rupture is unknown; however, the evidence for intervening in patients with small aneurysms has never been adequately demonstrated in a trial and there is no reason to think that the patients with coarctation will be significantly different in this respect. If most of these aneurysms are small and at low risk of rupture, screening may only serve to increase anxiety in patients with small aneurysms who do not end up having treatment and a large number of patients would have to be screened for a long period to make a difference in mortality.

Hemorrhagic stroke used to be a relatively common cause

of death in patients with coarctation of the aorta, but in the second half of the past century, only 1 patient with coarctation died of SAH in 30 years of follow-up of 880 operated patients,[29] compared with a 2.5% incidence of fatal IA rupture in the first half of the century.[7] The implication is that survival of patients with operated aortic coarctation is improving because surgery is being performed in younger patients, exposing the patient to fewer years of hypertension.[29] The effect of this is a reduction in the prevalence of IAs.[12,29] On the basis of these arguments, routine screening may not be justified to identify patients who need intracranial aneurysms by endovascular intervention.

There is, however, some evidence that rupture of IAs may occur earlier in patients with coarctation of the aorta than in the general population[21,30] and that treating hypertension may also reduce the risk of aneurysm rupture when an aneurysm is present. Identification of an IA may urge us to treat a patient's blood pressure aggressively and to caution them strongly against other risk factors for the development of IAs, such as smoking. Moreover, the standard treatment for native and recoarctation of the aorta is balloon dilation of the coarctation and stent placement.[31] There is a theoretic potential risk of IA rupture in increasing cerebral perfusion pressure by occluding the aorta, albeit temporarily. Surely an awareness of the presence of an IA will inform our management of the patient?

IAs and Hypertension

There are 2 theories as to why patients with aortic coarctation develop IAs. The first suggests that there is a common inherited pathogenic factor responsible for the 2 lesions,[32,33] and the second implicates inadequately controlled hypertension as the main cause.[8] Hypertension is a known risk factor for the development of IAs,[34,35] multiple IAs, and their rupture.[1] Furthermore, surges in blood pressure can further increase the growth of IAs.[33] In heritable conditions in which IAs are common such as adult polycystic kidney disease, hypertension is also a highly relevant risk factor.[34-36] In our study, there was no relationship between a single clinic blood pressure recording and aneurysms, though a diagnosis of hypertension, as documented in the notes, appeared to confer a risk.

Given that predictors of survival in coarctation are age at operation and blood pressure at first postoperative visit,[37] it is likely that the degree and duration of high blood pressure affects cerebral anatomy and autoregulation of cerebral blood flow,[26] increasing the likelihood that IAs will develop. Early detection and treatment of hypertension is key. Blood pressure control should perhaps be stricter for young patients than that proposed by guidelines aimed at older adults.

Limitations

Our cohort was chosen by looking at all patients with coarctation who underwent brain MRA scanning at the time of aorta scanning. Although the cohort was not selected, it may not be truly representative of all patients with coarctation of the aorta. Some patients may have been missed or lost to follow-up. However, during the period of this study, all scanning on patients with coarctation of the aorta in the Southwest of England was performed in our center, including that in all patients whose care had been recently transferred from pediatric cardiac services. We routinely scan all our patients with coarctation of the aorta every 5 years, and no patient was included twice in the study.

Any study of this sort is limited by relatively small numbers. However, relatively unselected sequential patients with coarctation have been scanned by using a sensitive diagnostic technique during an 8-year period. The study group is, therefore, likely to be more representative of patients with coarctation than previous prospective studies[11] in which patients have been invited for screening. This study does not address the issue of how frequently it is necessary to perform MRA to diagnose clinically significant IAs, nor does it provide evidence on the rate of growth of existing IAs.

It is possible to falsely identify IAs on MRA. MRA is flow-dependent, and errors can occur, albeit rarely. Conversely MRA can miss aneurysms of $\leq$3 mm.

Conclusions

Patients with coarctation of the aorta have a high prevalence of small intracranial aneurysms, which occur at an early age. Most aneurysms are small and likely to be at low risk of rupture. The benefit of screening is not clear, and interventional treatment of aneurysms identified by screening is likely to be marginal at best. Patients are significantly younger than those in other cohorts with IAs; if screening is to be performed, the usual screening in middle age may not be appropriate. Whether interventional treatment of IAs identified by screening is appropriate will only be clarified by further studies. In the meantime, this study does underline the importance of treating other risk factors, and our practice is to continue to screen for IAs, and to focus on controlling these risk factors aggressively in affected patients.

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