Prevalence of cerebral aneurysms in patients with fibromuscular dysplasia: a reassessment

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Object. The aim of this study was to determine the prevalence of cerebral saccular aneurysms in patients with carotid artery and/or vertebral artery (VA) fibromuscular dysplasia (FMD).

Methods. A metaanalysis was performed using data from 17 previously reported series of patients with internal carotid artery (ICA) and/or VA FMD that included information on the prevalence of cerebral aneurysms. In addition, the authors retrospectively evaluated their own series of 117 patients with ICA and/or VA FMD to determine the prevalence of cerebral aneurysms. The metaanalysis of the 17 earlier series, which included 498 patients, showed a 7.6 ± 2.5% prevalence of incidental, asymptomatic aneurysms in patients with ICA and/or VA FMD. In the authors’ series of patients with FMD, 6.3 ± 4.9% of patients harbored an incidental, asymptomatic aneurysm. When the authors’ series was combined with those included in the metaanalysis, the prevalence was found to be 7.3 ± 2.2%. The prevalence of aneurysms in the general population would have to be greater than 5.6% for there to be no statistically significant difference (chi-square test, p < 0.05) when compared with this 7.3% prevalence in patients with FMD.

Conclusions. The prevalence of intracranial aneurysms in patients with cervical ICA and/or VA FMD is approximately 7%, which is not nearly as high as the 21 to 51% prevalence that has been previously reported.

Key Words • cerebral aneurysm • fibromuscular dysplasia

The prevalence of intracranial saccular aneurysms in patients with internal carotid artery (ICA) and/or vertebral artery (VA) fibromuscular dysplasia (FMD) has been reported to be 21 to 51%. Although imaging studies performed to determine the prevalence of incidental aneurysms in the general population have excluded patients presenting with subarachnoid hemorrhage (SAH) or other symptoms caused by aneurysms, this bias has remained uncorrected with regard to the prevalence of aneurysms in patients who have FMD. Retrospective analyses of the prevalence of aneurysms in patients with FMD have been performed without regard to the selection bias that is introduced by the fact that patients who harbor aneurysms undergo cerebral angiography more frequently than patients who do not harbor aneurysms; this occurs because symptoms produced by the aneurysm often lead the patient to seek an angiographic examination. The high prevalence of aneurysms reported in patients with FMD is falsely elevated because most of the patients with aneurysms in these series underwent angiography in response to indications of SAH, and FMD was an incidental finding in these cases.

After eliminating a selection bias that favors inclusion of cases with aneurysm over cases without aneurysm, we calculated the prevalence of cerebral aneurysms in patients with FMD. We performed a metaanalysis by using data from previously reported series of patients with ICA and/or VA FMD that included information on the prevalence of cerebral aneurysms. We also retrospectively evaluated our own series of patients with FMD to determine the prevalence of aneurysms in patients with ICA and/or VA FMD.

Clinical Material and Methods

We performed a computer search of the literature (Medline; National Library of Medicine, Bethesda, MD) to find series of patients with FMD to include in a metaanalysis. Series were included if they provided information on aneurysm prevalence and specified how many patients presented with SAH. Reports covering fewer than four cases and series that had a bias toward inclusion of patients with aneurysms were excluded.

Seventeen published series of cervical ICA and/or VA FMD were found to be suitable for inclusion in the metaanalysis. In all series, the diagnosis of
Fibromuscular dysplasia and aneurysm

FMD was primarily based on angiographic studies; a small proportion of the series also offered pathological proof. There were 12 series,1,7,14,17,20,21,24,27,28,31,33,34 in which cases of FMD were reported without regard to presenting symptomatology or management, and five series,15,8,10,22 in which only cases referred for surgical evaluation of potential FMD-induced symptoms were reported. The completeness of angiographic evaluation was not specified in most of the series,17,24,27,34 although it was stipulated as covering fewer than three vessels in 16 of 37 cases in one series20 and in one of 15 cases in another.28

For each series used in the metaanalysis, we recorded the total number of patients, the number of patients with incidental and symptomatic aneurysms, and the number of patients with multiple aneurysms.

Using a computerized search of radiological and clinical databases at our institution, patient records from June 1978 to October 1996 were searched to identify patients with ICA and/or VA FMD. The diagnosis of FMD was based on angiographic findings in all 129 cases. The diagnostic criterion for FMD was the classic angiographic finding of a series of webs, often causing a corrugated or “string of beads” appearance, in the ICA and/or the VA.21,24,27 Because our study was designed to calculate the prevalence of aneurysms, we required that the patients selected had undergone angiographic evaluation that included bilateral ICA injections.

Nine patients were excluded because they had not undergone angiography of both ICAs. None of these nine patients was known to have an aneurysm. Lumbar puncture revealed possible SAH findings in three patients, but these findings were not confirmed on computerized tomography scanning or angiography. These three patients were excluded because it was unclear whether they may have harbored an angiographically occult aneurysm or only had experienced a traumatic lumbar puncture. Of the remaining 117 patients in the series, 18 patients underwent evaluation of both VAs, 79 patients underwent evaluation of one VA, and 20 patients underwent only bilateral ICA angiography with no VA angiography.

The angiography report in each case was reviewed with regard to the presence of an intracranial saccular aneurysm. The presence or absence of SAH or other symptoms produced by the aneurysm in each case was determined from the clinical records.

We collected additional data to evaluate the relationship between FMD and aneurysms apart from the prevalence of aneurysms in patients with FMD. The angiography report in each case was reviewed with regard to the number and location of intracranial saccular aneurysms and the location of FMD. The indication for angiography and the relationship of FMD to the patients’ presenting symptoms were recorded from the clinical records. Our neurosurgical clinical database was used to determine the number of aneurysms treated at our institution from 1978 to 1996.

From data acquired in the metaanalysis and from our own series, the prevalence of aneurysms was calculated before and after removal of cases of symptomatic aneurysms. The 95% confidence interval for each prevalence rate was calculated. Using chi-square analysis, we calculated the threshold for the prevalence of aneurysms in an age- and gender-matched control population, below which there would be a significant difference when compared with the prevalence of aneurysms in patients with FMD (p < 0.05).

Results

The 17 series selected for the metaanalysis included 498 patients ranging in age from 4 to 83 years. Of the cases in which gender was specified, 397 (85%) of 467 were female. One hundred eight patients (22%) harbored an aneurysm, of whom 76 presented with SAH. The prevalence of aneurysms in patients with FMD in the metaanalysis was 7.6 ± 2.5% (95% CI) after patients who presented with SAH were excluded (Table 1).

The series of 117 patients with FMD at our institution included 108 women and nine men, aged 31 to 88 years (mean 60 years). Twenty eight patients (24%) harbored an aneurysm, 22 of whom presented with aneurysm-induced symptoms (19 patients with SAH and three with cranial nerve deficits) that prompted us to perform an angiographic examination. Of the 28 patients who harbored aneurysms, 25 were women and three were men. Excluding the patients with symptomatic aneurysms from the population, six (6.3 ± 4.9%) of 95 patients with FMD had an incidental aneurysm (Table 1). Of these six patients with asymptomatic aneurysms, five were women and one was a man.

By combining the patients in the metaanalysis with the patients in our series, we found the prevalence of incidental, asymptomatic aneurysms to be 7.3 ± 2.2%. The prevalence of aneurysms in the general population would have to be greater than 5.6% for there to be no statistically sig-
significant difference (chi-square, p < 0.05) when compared with this 7.3% prevalence in patients with FMD. The published data from the literature regarding prevalence of cerebral aneurysms in the general population is discussed later in this report.

We evaluated other data obtained from our series to assess the relationship between FMD and aneurysm further. Between 1978 and 1996, 1084 aneurysms were treated in our hospital; only 28 (2.6%) were found in patients who had FMD. In 1993 and 1994, 1010 diagnostic angiographic studies were performed in our hospital and 194 cerebral aneurysms were treated. If one does not account for the selection bias of patients presenting with symptoms caused by an aneurysm, one could calculate the prevalence of aneurysms to be 19% in the general population, which is not significantly different (chi-square test, p > 0.10) from the uncorrected prevalence of 24% in our series of patients with FMD. In our series, FMD was an incidental finding (asymptomatic) in 67% of patients, not clearly related to symptoms in 20%, and symptomatic (ischemic symptoms related to arterial stenosis or occlusion) in 13%.

Thirty-six aneurysms were identified in 28 patients, six (21%) of whom harbored multiple aneurysms. The distribution of the aneurysms was as follows: nine in the anterior communicating artery, seven in the posterior communicating artery, seven in the ophthalmic artery, four in the supraclinoid ICA, five in the middle cerebral artery, two in the basilar tip, four in the cavernous carotid artery, and one in the anterior choroidal artery. Angiography revealed no dysplasia at the site of the intracranial aneurysms.

In the patients who had FMD but no aneurysm, 153 (63%) of 241 vessels evaluated by means of angiography were affected by FMD. In the patients who had FMD and aneurysms, 50 (56%) of 90 vessels evaluated with angiography were affected by FMD. The location of the aneurysm did not seem to relate to the location of the FMD: the two patients who had aneurysms in the posterior circulation had FMD only in the anterior circulation; one patient who had an aneurysm in the anterior circulation had FMD only in the VA; and five patients who had aneurysms in the anterior circulation had FMD only in the contralateral carotid artery.

Discussion

We found a 7.3% prevalence of incidental, asymptomatic cerebral aneurysms in patients who had ICA and/or VA FMD. This is much lower than the prevalence of 21 to 51% previously reported in the literature.\textsuperscript{10,20,24,27,28,29} If one does not account for the selection bias of patients presenting because of symptoms caused by an aneurysm, one could calculate the prevalence of aneurysms in patients with FMD in our series to be 24%, which is similar to the high prevalence reported in the literature, but which is not significantly different (chi-square, p > 0.10) from the 19% prevalence of aneurysms in our general population of all patients undergoing cerebral angiography.

Imaging studies designed to determine the prevalence of aneurysms in the general population have excluded patients who presented with SAH or other symptoms caused by aneurysms;\textsuperscript{11,12,25} however, until now this bias has remained uncorrected with regard to the prevalence of aneurysms in patients who have FMD. We contend that retrospective angiographic data used to calculate the prevalence of cerebral aneurysms in patients with FMD should be limited to patients who present for angiography because of symptoms or signs unrelated to cerebral aneurysms, which would eliminate selection bias.

Because an unselected, cross-sectional sample of the general population does not undergo cerebral angiography, the precise numbers of patients with and without FMD and with and without aneurysms can never be absolutely determined. Therefore, we must rely on an estimation of the prevalence of aneurysms in patients with FMD, based on data obtained in people who do undergo cerebral angiography. In previous reports, the true prevalence of aneurysms in patients with FMD is not what has been measured, but rather the high background prevalence of aneurysms in the overall population of patients who undergo angiography; that is, if 25% of all patients who undergo angiography have SAH as an indication, approximately 25% of the patients in this population with any given underlying disease such as FMD would be expected to harbor a cerebral aneurysm. A prevalence of aneurysms in one population that was determined without regard to aneurysm symptoms cannot be validly compared with a prevalence of aneurysms in another population that was determined after excluding patients with symptoms of aneurysm. Because the best estimates of the prevalence of cerebral aneurysms in the general population were determined by excluding patients with symptomatic aneurysms,\textsuperscript{3,13,22} estimates of aneurysm prevalence in selected populations such as patients with FMD should be determined in this manner to allow for a valid comparison to the general population.

How significantly different the prevalence of aneurysms in patients with FMD is from the general population depends on which number one accepts as the true prevalence of aneurysms in the general population. In autopsy series, the prevalence of saccular cerebral aneurysms in adults has been reported to be between 1.5% and 8%.\textsuperscript{3,12,16,20} In an angiographic series reported by Atkinson, et al.,\textsuperscript{4} the prevalence of cerebral aneurysms in the general population was 1% in the United States. However, the authors of that series underestimate the prevalence of aneurysms for the following reasons: 1) only the anterior circulation was evaluated, which underestimates the prevalence of cerebral aneurysms by 5%\textsuperscript{15,16} to 20%\textsuperscript{1} by excluding posterior circulation aneurysms; 2) 10% of the patients were younger than 31 years of age, including numerous children, which underestimate the prevalence of aneurysms in adults because saccular cerebral aneurysms are acquired and quite rare in children and young adults;\textsuperscript{5,12,20,30,\textsuperscript{3}} 3) only patients who were free of all other vascular disease (including atherosclerosis) were included, which may result in an underestimated prevalence because atherosclerosis may be a significant risk factor for cerebral aneurysm formation;\textsuperscript{30} and 4) 55% of the patients were men, which could further underestimate the prevalence of aneurysms because of the higher prevalence of aneurysms in females, as explained later. Additionally, in the series conducted by Atkinson, et al.,\textsuperscript{4} three aneurysms were found in only 278 patients, which is a rather small sample size and, therefore, is not highly statistically reliable.

The preponderance of females among patients with
Fibromuscular dysplasia and aneurysm

FMD may account for an increase in the prevalence of aneurysms when compared with the prevalence in a general population that includes both males and females. In our series, 92% of the patients were women; previously women were reported to account for 85% of patients with ICA and/or VA FMD. Women represent approximately 60% of all patients with cerebral aneurysm who present with SAH, making the prevalence of ruptured aneurysms in females approximately 1.5 times greater than in males. As such, the female predominance in patients who have FMD can account for as much as a 30% increase in cerebral aneurysms relative to the general population. The autopsy study by Chason and Hindman found the prevalence of aneurysms in males to be 3.5%; however, the prevalence in females was 7.2%, which is quite similar to the prevalence of aneurysms in patients with FMD in our study. However, theirs was an autopsy study that included aneurysms as small as 1 mm. An angiographic study such as ours undoubtedly is less sensitive than such an autopsy study; thus, we cannot make a precise comparison.

Other than the study by Atkinson, et al., the only other imaging studies in the literature are two series from Japan in which a 5 to 6% prevalence of incidental aneurysms is reported in the general population. However, it is probably not accurate to compare patients with FMD in Japan with those in the United States because there may be an overall higher prevalence of aneurysms in the Japanese. The prevalence of death caused by SAH in the Japanese population is approximately 1.5 times greater than that in the American population.

A review of the published angiographic and autopsy series discussed above demonstrates that the prevalence of aneurysms in the general population is not yet precisely defined and interpretation of the existing literature requires careful attention to the methodological details of the studies. Based on an analysis of the series by Atkinson, et al., and the two imaging series from Japan, the true prevalence of incidental aneurysms found on angiography in the American population is probably more than 1% and less than 5%; however, this number may have to be multiplied by a factor as great as 1.3 for a population that is nearly all women. The prevalence of aneurysms in an age- and gender-matched population would have to be greater than 5.6% for there to be no statistically significant difference (chi-square test, p < 0.05) when compared to a 7.3% prevalence in patients who have FMD.

The prevalence of carotid FMD in patients undergoing cerebral angiography is between 0.25% and 3.7%. We identified FMD in 2.6% of patients treated for aneurysm at our institution, which is not different from the prevalence in the general population. The prevalence of FMD in patients who have suffered an SAH from aneurysm rupture would be expected to be higher than that found in the general population if the prevalence of incidental aneurysms in patients with FMD is increased. An exception to this would be if aneurysms associated with FMD were accompanied by a higher prevalence of SAH than aneurysms in the general population; however, there is no evidence that this is the case. George and colleagues found a 30% prevalence of FMD in patients who harbored cerebral aneurysms and had SAH. The reason for the very high prevalence of FMD in that series is unclear; perhaps the researchers used a very low threshold for diagnosing FMD angiographically.

The prevalence of multiple intracranial aneurysms in patients with FMD has been reported as being excessively high at 33 to 71%. More than one intracranial aneurysm is found in 15 to 20% of all cases in the general population. We found that 22% of patients who had FMD and aneurysms had multiple aneurysms. Our data indicate that there is little, if any, increased risk of multiple aneurysms in patients with FMD.

In addition to the prevalence of aneurysms in patients with FMD, we explored several other relationships between aneurysms and FMD. We found no relationship between the location of the FMD and the location of the aneurysm and no relationship between the severity of the FMD (as reflected by the number of vessels involved) and the prevalence of the aneurysms. We did not find an unusual distribution of aneurysms in our series of patients who had FMD.

Our study shows that there may be an increased prevalence of intracranial aneurysm in patients with cervical ICA and/or VA FMD; however, if this increased prevalence exists, it is not nearly as high as has been previously reported. Diagnosis in almost all patients with cervical ICA and/or VA FMD is made with the aid of cerebral angiography and, therefore, the prevalence in the general population would be expected to be higher than that found in the Japanese. This is probably why there has not been discussion of screening FMD patients as there has been for polycystic kidney disease. Completion of four-vessel angiography in patients found to have carotid or VA FMD has been previously recommended; however, it remains unclear as to whether this is necessary. What also remains to be determined is the utility of screening for intracranial aneurysms in patients whose FMD affects vessels other than the ICA and VA because FMD may be a systemic disease. The cause of FMD is unclear; however, because it often affects multiple vessels in scattered parts of the body, it is probably caused by a systemic process and, perhaps, is influenced by genetic and hormonal factors. If an increased prevalence of aneurysms in patients with FMD were to be proven and if the prevalence were sufficiently high to justify screening examinations, consideration should be given to using magnetic resonance angiography or computerized tomography angiography to screen patients whose FMD affects arteries other than the ICA and the VA.

References


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