Marfan Syndrome Is Not Associated With Intracranial Aneurysms

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Background and Purpose—It has been proposed that patients with Marfan syndrome have an increased prevalence of intracranial aneurysms. This proposition is based on 10 clinical reports, 1 pathology case, and an autopsy series of 7 patients. By contrast, 5 clinical series of Marfan patients have failed to document any such relationship. We present our institution’s autopsy and clinical experience with Marfan syndrome and analyze in our patient population the purported association between this condition and intracranial aneurysms.

Methods—The results of an autopsy series at the Johns Hopkins Hospital of 25 confirmed Marfan syndrome patients from 1939 to the present were reviewed retrospectively. The prevalence of intracranial aneurysms in this Marfan syndrome autopsy series was compared with that in the autopsy population at this institution and with that in the general autopsy population as reported in the literature. In addition, the prevalence of Marfan syndrome in a recent neurosurgical series of 710 consecutive aneurysm cases (1990–1998) was determined.

Results—Of the 25 autopsy cases, only 1 had evidence on autopsy of an unruptured, 2-mm aneurysmal dilatation at the anterior communicating artery complex. Three autopsy patients suffered intracranial hemorrhages but had negative angiography and postmortem examinations for intracranial aneurysms. The remaining 21 patients had negative autopsies for intracranial hemorrhages or intracranial aneurysms. The neurosurgical series of 710 patients treated for intracranial aneurysms did not include any patient with Marfan syndrome.

Conclusions—The prevalence of 1 patient of 25 with an intracranial aneurysm is not statistically different from the 1.3% prevalence of intracranial aneurysms in the autopsy population at this institution (P=0.24) or from the 2.0% prevalence of intracranial aneurysms in the general autopsy population (P=0.31). We therefore conclude that there exists no evidence that Marfan syndrome is associated with an increased prevalence of intracranial aneurysms. (Stroke. 1999;30:1632-1636.)

Key Words: cerebral aneurysm • Marfan syndrome • prevalence

Marfan syndrome is an autosomal dominant, connective tissue disorder caused by mutations in the gene encoding fibrillin-1 (FBN1, chromosome 15q21).1–4 Fibrillin-1 is a glycoprotein found in extracellular microfibrils,5 which are important structural components of the extracellular matrix.4,5 As such, extracellular microfibrils are an essential structural component of tissues in the skeletal, ocular, cardiovascular, pulmonary, integumentary, and central nervous systems.5,6 Therefore, fibrillin-1 abnormalities in these organ systems give rise to the characteristic manifestations of Marfan syndrome.2

The diagnosis of Marfan syndrome is based on specific clinical and, most recently, genetic criteria. The diagnostic criteria have been refined since the condition was first described in a 5-year-old girl in 1896 by Antoine Bernard-Jean Marfan, a French professor of pediatrics.7,8 After Marfan’s original description, other manifestations of the syndrome were recognized and subsequently codified in 1955 by McKusick at Johns Hopkins.9,10 In 1986, during the 7th International Congress of Human Genetics in Berlin, Germany, a panel of experts agreed on the specific clinical criteria for the diagnosis of Marfan syndrome.2 These criteria have been widely adopted and are known as the “Berlin nosology.” Recently, De Paepe and colleagues8 proposed more stringent clinical criteria and recommended that genetic information be considered for the diagnosis.

Over the past 30 years, an association between Marfan syndrome and intracranial aneurysms has been repeatedly proposed but also vigorously challenged. This association has been based on 10 clinical reports of Marfan patients with intracranial aneurysms,11–20 1 pathology report describing the early development of an intracranial aneurysm in a Marfan patient,21 and 1 autopsy series of 7 Marfan patients, 2 of whom had intracranial aneurysms.22 By contrast, no association between Marfan syndrome and intracranial aneurysms has been found in 5 clinical series of Marfan patients.23–27
Given the prognostic concerns associated with the presence of an intracranial aneurysm, the proposed increased prevalence of these lesions in Marfan syndrome has raised the question of whether Marfan patients should be evaluated to rule out an intracranial aneurysm.

Our institution has had a dedicated program for patients with Marfan syndrome since the 1950s. Under the direction of McKusick and colleagues, 300 new or established Marfan patients are seen annually at the Johns Hopkins Hospital, and more than 1400 Marfan patients have been evaluated and treated in this program since its inception. As such, there is a large institutional experience with the treatment of complications of Marfan syndrome. We have drawn on our pathological and clinical experience with Marfan syndrome to analyze the purported association between Marfan syndrome and intracranial aneurysms. In this study we report the prevalence of intracranial aneurysms in our autopsy series of 25 Marfan patients (1939–1996), and in addition we report the prevalence of Marfan syndrome in our recent neurosurgical series of 710 consecutive intracranial aneurysm cases (1990–1998).

Subjects and Methods

Diagnostic Criteria for Marfan Syndrome

A primary analysis was performed with the use of the diagnostic criteria detailed in the Berlin nosology to establish the diagnosis of Marfan syndrome in our autopsy and clinical series. Using the Berlin nosology, we were then able to compare our results with those of the most recent autopsy and clinical studies that have analyzed the association of Marfan syndrome and intracranial aneurysms. As presented in the Berlin nosology, the diagnostic manifestations of Marfan syndrome include specific skeletal, ocular, cardiovascular, pulmonary, integumentary, or central nervous system findings. If a primary relative has Marfan syndrome, the requirements for diagnosis of Marfan syndrome are simplified. In addition, a major manifestation must be present in either organ system. Intracranial examinations were performed in 44 of these autopsies. Of these 44 cases, only 25 fulfilled the criteria for Marfan syndrome.

Autopsy Series

The pathology autopsy database of the Johns Hopkins Medical Institutions consists of more than 50 000 reports of all autopsies performed at the institution during 1889–1998. This database was searched to identify potential Marfan cases with the key words Marfan, ectopia lentis, and arachnodactyly. The medical records and autopsy results of all potential Marfan patients were reviewed. Epidemiological information recorded included the patients’ sex, age of death, race, and the presence of a family history of Marfan syndrome. Characteristic manifestations of Marfan syndrome, specifically skeletal, ocular, cardiovascular, pulmonary, integumentary, and central nervous system manifestations, were recorded. The Berlin nosology and the De Paepe criteria were then applied to the cases to select those that fulfilled the diagnostic criteria for Marfan syndrome by either system. Intracranial autopsy results from Marfan patients and histological specimens of reported intracranial aneurysms were reviewed.

Neurosurgical Series

The Johns Hopkins Hospital neurosurgical series of patients treated for intracranial aneurysms consists of all patients admitted to the Johns Hopkins Hospital, Baltimore, Md, and the Johns Hopkins Bayview Medical Center, Baltimore, Md, with an angiographically or autopsy-proven diagnosis of an intracranial aneurysm. The study period was from January 1990 to December 1998. Medical records of the patients were reviewed to identify either characteristic manifestations of Marfan syndrome as described above or a previous diagnosis of Marfan syndrome, according to the Berlin nosology or the De Paepe criteria.

Statistical Analysis

The epidemiological prevalence of intracranial aneurysms in the population in general and in the Hopkins series in particular was compared with the prevalence of intracranial aneurysms in our Marfan autopsy series. The binomial probability test was applied with the use of Stata statistical software for the Macintosh (version 4.0, Stata Corporation). The power of the study was determined with the same statistical software.

Results

Marfan Syndrome Autopsy Series: Primary Analysis Using the Berlin Nosology

The search of the autopsy database identified 57 potential Marfan patients. Intracranial examinations were performed in 44 of these autopsies. Of these 44 cases, only 25 fulfilled the Berlin nosology criteria for the diagnosis of Marfan syndrome. These 25 patients were members of 24 different families and died during 1939–1996. The epidemiological characteristics of these patients, including their sex, age of death, cause of death, and family history of Marfan syndrome, are listed in Table 1. The manifestations of Marfan syndrome in these patients are summarized in Table 2. Skeletal manifestations of Marfan syndrome were present in 23 patients (92%); the 2 patients (8%) without skeletal findings had a first-degree relative with Marfan syndrome.

Ocular manifestations were observed in 17 patients (68%), cardiovascular manifestations in 25 patients (100%), pulmonary manifestations in 2 patients (8%), and integumentary manifestations in 9 patients (36%).
Of the 25 patients in the autopsy series, only 1 patient had evidence on autopsy of an intracranial aneurysm. The aneurysm was an asymptomatic, unruptured, 2-mm dilatation at the anterior communicating artery complex (Figure). This patient was a black man who had a positive family history of Marfan syndrome and died in 1955 of an aortic dissection at the age of 30 years. Other Marfan syndrome manifestations exhibited by the patient included arachnodactyly, hyperextendable joints, and dilatation of the ascending aorta. Cystic medial necrosis was observed on histological examination of the aorta. Microscopic histological examination of the intracranial aneurysm as it originated from the parent vessel revealed fragmentation and thinning of the medial smooth muscle layer at the aneurysm neck and absence of the media at the aneurysm body and dome with replacement of this region with thin, fibrous connective tissue.

Although an additional 3 patients in the autopsy series experienced intracranial hemorrhages, by autopsy none were aneurysmal subarachnoid hemorrhages. One male patient died at the age of 50 years as a result of a cerebellar hematoma that was a complication from surgical resection of an acoustic schwannoma. Another male patient, who died at the age of 21 years from complications of aortic valve and aortic graft surgery, had previously experienced a right frontal hemorrhage while taking warfarin. Cerebral angiography had ruled out an intracranial aneurysm. A female patient died at the age of 37 years from a posterior fossa hemorrhage while taking warfarin. She also had developed a T11-L5 intradural hematoma 4 days before her death. The source of the intracranial hemorrhage could not be identified, but an aneurysm was ruled out at autopsy.

Marfan Syndrome Autopsy Series: Secondary Analysis Using the De Paepe Criteria
As described above, De Paepe and colleagues recently proposed more stringent clinical criteria for the diagnosis of Marfan syndrome. With the use of these modified criteria, 4 of the 25 patients in the autopsy series would have been excluded. One of these patients would have been the patient with the anterior communicating artery aneurysm. Therefore, using the modified criteria for the diagnosis of Marfan syndrome would have resulted in no cases of intracranial aneurysms in our autopsy series and strengthened the conclusions of this report.

Aneurysm of the anterior communicating artery complex identified at autopsy in 1 patient in the present autopsy series. The 2-mm lesion was observed in a 30-year-old male Marfan patient who died in 1955 from dissection of an aortic aneurysm. Microscopic histological examination of the aneurysm revealed thinning of the smooth muscle in the media at the aneurysm neck and distal absence of the media with replacement of this region with thin, fibrous connective tissue.

Statistical Analysis
In the literature, the best estimate for the prevalence of intracranial aneurysms in the general population is approximately 2%, which is based on the combined results of Bannerman’s review of 8 autopsy series of 51 360 patients. At our institution, we have previously reported the prevalence of intracranial aneurysms in our autopsy population as 1.3%. In our Marfan autopsy series, the prevalence of intracranial aneurysms was 1 of 25 patients. There is no statistically significant difference between the prevalence of intracranial aneurysms in our Marfan autopsy sample and that reported either in the general autopsy population (P=0.31, binomial probability test) or in our institution (P=0.24, binomial probability test).

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>No. of Patients (%)</th>
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<tbody>
<tr>
<td>Skeletal</td>
<td>23 (92%)</td>
</tr>
<tr>
<td>Arachnodactyly</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>Anterior chest wall deformity</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>Ocular</td>
<td>17 (68%)</td>
</tr>
<tr>
<td>Ectopia lentis</td>
<td>14 (56%)</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>25 (100%)</td>
</tr>
<tr>
<td>Dilation of aortic root</td>
<td>22 (88%)</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>12 (48%)</td>
</tr>
<tr>
<td>Aortic insufficiency</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>Medial necrosis of the aorta</td>
<td>18 (72%)</td>
</tr>
<tr>
<td>Pulmonary (spontaneous pneumothorax)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Integumentary (hernia)</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

TABLE 2. Manifestations of Marfan Syndrome Observed in 25 Autopsy Patients
The prevalence of intracranial aneurysms was 0 of 21 Marfan patients when the more specific criteria of De Paepe were used to determine a Marfan diagnosis. Again, a statistically significant difference does not exist between the prevalence of intracranial aneurysms in this Marfan autopsy series and that reported in the general autopsy population ($P=0.65$, binomial probability test) or in our institution ($P=0.76$, binomial probability test).

The size of this autopsy series was probably not large enough to detect small differences, either increases or decreases, in the prevalence of intracranial aneurysms in the Marfan autopsy series compared with that in the general population. This study did, however, possess sufficient power (0.99) to determine whether the alternative prevalence of intracranial aneurysms in Marfan patients (29%) that was reported by Schievink et al$^{22}$ is the true prevalence of intracranial aneurysms in Marfan patients.

**Neurosurgical Series**

None of the 710 patients treated for intracranial aneurysms at the Johns Hopkins Hospital in the past 9 years had Marfan syndrome.

**Discussion**

Although several investigators have either stated or implied that patients with Marfan syndrome have an increased prevalence of intracranial aneurysms, this association remains questionable. To our review, it seems that the proposed association of Marfan syndrome and intracranial aneurysms is based on the following: (1) 10 case reports,$^{11–20}$ (2) 1 pathology report describing the early development of an intracranial aneurysm in a Marfan patient,$^{21}$ and (3) 1 autopsy series of 7 Marfan patients, 2 of whom had intracranial aneurysms.$^{22}$ Further scrutiny of these studies, however, reveals several problems. Of the 10 cases described in the individual case reports, 4 do not meet the diagnostic criteria of the Berlin nosology.$^{12,13,16,20}$ In the pathology report of Stehbens and colleagues,$^{21}$ the mural thinning described at 2 bifurcations of the right middle cerebral artery in a Marfan patient is a common finding in a minority of normal subjects and is not absolutely correlated with the development of an aneurysm.$^{30}$ Finally, the autopsy series reported by Schievink and colleagues$^{22}$ from the Mayo Clinic in Rochester, Minn., might suffer from a sampling bias in cerebrovascular cases that has been previously recognized and reported by this group.$^{31}$ Since the Mayo Clinic is a major referral center for intracranial vascular lesions, this referral pattern might have introduced a selection bias in the small autopsy series of 7 cases.

By contrast, 5 clinical studies have failed to identify an association between Marfan syndrome and intracranial aneurysms.$^{23–27}$ Murdoch and colleagues$^{23}$ from Johns Hopkins reported the cause of death in 56 of 74 deceased Marfan patients and did not identify an intracranial aneurysm or subarachnoid hemorrhage in any of these patients. In addition, a symptomatic intracranial aneurysm was not reported in any patient. Pyeritz and McKusick,$^{24}$ also from Johns Hopkins, reported the clinical manifestations of Marfan syndrome in 50 consecutive patients and did not identify any patients with a symptomatic intracranial aneurysm. Van den Berg and colleagues$^{27}$ specifically addressed the association between Marfan syndrome and intracranial aneurysms in a series of 129 Marfan patients with 581 observation years and did not find evidence for such an association. In addition, a diagnosis of Marfan syndrome was not established in any of the 826 patients admitted to their institution’s neurology and neurosurgery services with the diagnosis of a subarachnoid hemorrhage or intracranial aneurysm.$^{27}$

Our institution has had a dedicated program for patients with Marfan syndrome since the 1950s in which more than 1400 Marfan patients have been evaluated and treated since its inception.$^{9,24}$ We therefore have a large institutional experience with the treatment of complications of Marfan syndrome and have noticed a paucity of Marfan patients with intracranial aneurysms. Two clinical studies of these Marfan patients by Murdoch et al$^{23}$ and Pyeritz and McKusick$^{24}$ failed to identify any Marfan patient with a symptomatic intracranial aneurysm. Our autopsy series of 25 Marfan cases has only 1 case with an intracranial aneurysm, which is consistent with the expected prevalence of intracranial aneurysms in the general population and in our autopsy population. Similarly, our neurosurgical series of 710 aneurysm cases does not include any patient with Marfan syndrome. We therefore conclude that there exists no evidence that Marfan syndrome patients are at an increased risk for the development of intracranial aneurysms.

It is of interest that the 1 Marfan syndrome patient in our study who had an intracranial aneurysm had a brother who was also affected by Marfan syndrome. The brother underwent an autopsy as well and was not found to have an intracranial aneurysm. This patient died from a dissection of the ascending aorta and was aged 35 years at his time of death, 5 years older than the age at which his sibling who possessed the aneurysm died. Since this patient did not have an intracranial aneurysm, one could argue that his brother’s aneurysm was probably sporadic and not a phenotypic manifestation of the specific FBN1 mutation carried by the brothers.

In regard to the 2 patients who had intracranial hemorrhages while taking warfarin, the evidence strongly suggests that neither of these hemorrhages was caused by a ruptured intracranial aneurysm. The first patient presented with an intraparenchymal hemorrhage in the frontal lobe. There was no subarachnoid hemorrhage. This would be a rare presentation for a ruptured saccular aneurysm but is a well-described complication of warfarin anticoagulation therapy. In addition, a 4-vessel angiogram did not reveal an aneurysm, and an intracranial aneurysm was not discovered during a detailed examination of the intracranial vasculature at autopsy. The second patient initially presented with a T11-L5 subdural hematoma. Neither an aneurysm nor an arteriovenous malformation was identified by angiography. This patient then underwent surgical decompression and evacuation of the spinal subdural hematoma. The source of the hemorrhage was not identified during surgery. The patient died poorly postoperatively, and a CT scan revealed further bleeding into the posterior fossa. The patient died and had a thorough intracranial examination at autopsy. Although the vertebral and
basilar arteries were described as “ectatic and tortuous,” a saccular aneurysm was not observed in any part of the vasculature. Even though a small or compressed aneurysm may not be detected by angiography, the clinical and post-mortem findings in these cases strongly suggest that aneurysmal ruptures were not the cause of the hemorrhage in either case. Furthermore, it would be unlikely that even a small aneurysm would not be identified at autopsy, especially since an aneurysmal source of hemorrhage was specifically sought in each case.

The absence of aneurysm patients with Marfan syndrome in our neurosurgical series of 710 patients and the series of 826 patients reported by van den Berg and colleagues is probably explained by the early age of death of most Marfan patients. In our autopsy series the mean and median ages at time of death were 39 and 38 years, respectively. By contrast, the sixth decade, with typical mean and median ages at the time of presentation of 56 and 59 years, respectively.32 Therefore, the few Marfan patients with preaneurysmal defects probably die from other causes before they develop a mature aneurysm that ruptures.

We conclude that there exists no evidence that Marfan syndrome and related disorders are a cause of aneurysms in Marfan’s syndrome. This conclusion implies that the already extensive and costly evaluations pursued in these patients do not need to include serial intracranial radiographic studies intended to rule out these lesions.

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References

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