Is Marfan Syndrome Associated With Symptomatic Intracranial Aneurysms?

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Background and Purpose Marfan syndrome is a heritable disorder of connective tissue caused by a deficiency of the glycoprotein fibrillin. In several publications and neurological textbooks, a relationship between Marfan syndrome and intracranial aneurysms has been assumed.

Methods The records of 135 patients classified as having Marfan syndrome who visited the Amsterdam Marfan clinic or were admitted to the departments of neurology and neurosurgery and the records of all patients with a subarachnoid hemorrhage or intracranial aneurysm who visited or were admitted to the departments of neurology and neurosurgery between January 1, 1982, and January 1, 1994, were retrieved. The literature was reviewed regarding Marfan syndrome and intracranial aneurysms.

Results No patient visiting the Marfan clinic had a symptomatic intracranial aneurysm. No patient with Marfan syndrome had been admitted with a ruptured intracranial aneurysm at the departments of neurology or neurosurgery in this period, while during that period 826 patients with symptomatic intracranial aneurysms had been admitted. During follow-up of 129 of the 135 patients with Marfan syndrome (2850 retrospective patient observation years and 581 prospective patient observation years), none presented a symptomatic intracranial aneurysm. The suggested relationship between Marfan syndrome and intracranial aneurysms is based mainly on 10 case reports. However, the diagnosis of Marfan syndrome is doubtful in several of these reports. Several large studies of patients with Marfan syndrome did not mention a ruptured intracranial aneurysm as a clinical manifestation.

Conclusions We conclude that there is insufficient evidence to presume a relationship between symptomatic intracranial aneurysms and Marfan syndrome on the basis of currently available data. (*Stroke.* **1996;27:10-12.**)

Key Words • cerebral aneurysm • connective tissue disorders • glycoproteins • Marfan syndrome

Marfan syndrome is an inherited disorder of connective tissue characterized by manifestations of the musculoskeletal, ocular, and cardiovascular systems; it occurs with an estimated prevalence of 1 in 10 000.[1] Marfan syndrome is diagnosed on the basis of clinical manifestations that are strictly defined.[2,3] The cause is a defect in fibrillin, a glycoprotein that is a structural component of microfibrils found in many tissues.[1,4,5] Several textbooks and other publications have associated Marfan syndrome with intracranial aneurysms.[6-11] This relationship, if valid, may be of great pathogenic and clinical significance. Studies should be performed to elucidate the possible role of fibrillin in the pathogenesis of intracranial aneurysms, and screening of patients with Marfan syndrome to detect asymptomatic intracranial aneurysms might be warranted. Elective surgery in unruptured intracranial aneurysms has a low mortality and morbidity,[12] while mortality of ruptured intracranial aneurysms can be as high as 50%.[13-15]

The purpose of this study was to seek evidence for an increased incidence of intracranial aneurysms in patients with Marfan syndrome. We examined the prevalence of symptomatic intracranial aneurysms in a group of patients with Marfan syndrome, investigated the incidence of symptomatic intracranial aneurysms during follow-up, examined the prevalence of Marfan syndrome in patients with intracranial aneurysms admitted to the departments of neurology and neurosurgery, and reviewed the literature of the possible relationship between intracranial aneurysms and Marfan syndrome.

Subjects and Methods

In 1982 an outpatient clinic in Amsterdam was instituted for patients with Marfan syndrome and other connective tissue disorders (for both children and adults). At the first and subsequent visits, all patients are examined by a (pediatric) cardiologist, an ophthalmologist, an orthopedic surgeon, and a clinical geneticist. Over the years all patients were examined by a stable team of investigators using a standard protocol. From 1982 to 1986, Marfan syndrome was diagnosed with the use of the criteria defined by Pyeritz and McKusick.[3] Thereafter, the "Berlin nosology" was followed.[2] There are no large differences between these sets of criteria, and in retrospect we have also applied the Berlin criteria to the group of patients seen before 1986. All patients fulfilled these criteria. The records of all patients attending the Marfan clinic between January 1, 1982, and January 1, 1994, and classified as having Marfan syndrome were retrieved. We collected data on patients' age, sex, and clinical manifestations. During the follow-up period we searched for new manifestations of the disease.

In addition, we retrieved the records over the same period of all patients with Marfan syndrome who visited or were admitted to the departments of neurology and neurosurgery, both inpatients and outpatients.

For the literature review, we performed a Medline search using the following key words: Marfan syndrome, intracranial aneurysm, connective tissue disorder, and subarachnoid hemorrhage. We also followed all references from the articles thus found and traced the references on this topic from several textbooks.[6-8,10,11]

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TABLE 1. Major Presenting Manifestations in 135 Consecutive Patients With Marfan Syndrome

	No. of Patients
Skeletal	
Arachnodactyly	69
Anterior chest deformity	86
Scoliosis	39
Dolichostenomelia	47
Tall stature*	77
High arched palate	12
Hypermobile joints	30
Ocular	
Ectopia lentis	
Unilateral	13
Bilateral	55
Myopia	38
Iridodonesis	33
Iris transillumination	29
Retinal detachment	1
Cardiovascular	
Mitral valve prolapse	95
Aortic root dilatation	88
Dissection of the aorta	13
Dissection of the subclavian artery	1
Pulmonary	
Spontaneous pneumothorax	8
Skin and integument	
Striae distensae	49
Inguinal hernia	11
Umbilical hernia	2
Diaphragmatic hernia	1
Nervous system	
Lumbosacral meningocele	2

*Height >98th percentile.

Results

The patient group comprised 135 patients (63 male and 72 female). The mean age at first presentation was 21.1 years, ranging from 1 to 69 years. The presenting manifestations of all patients are listed in Table 1. No patient with Marfan syndrome had a history of a subarachnoid hemorrhage or had presented symptoms relating to an intracranial aneurysm at the first visit to the Marfan clinic.

In 129 patients, with a mean age of 21.3 years, we obtained a follow-up (mean follow-up, 4.5 years; range, 7 months to 12 years). This resulted in a total of 581 observation years. Complications that developed during the follow-up are listed in Table 2. During the follow-up 6 patients died; in 4 this was caused by a dissection of the ascending aorta, and in 2 the cause was unknown.

During follow-up, one patient experienced an intracerebral hemorrhage. The 37-year-old patient was admitted for alcohol and barbiturate intoxication. At the age of 34 years Marfan syndrome had been diagnosed on the basis of an anterior chest deformity, scoliosis, dolichostenomelia, striae distensae, spontaneous pneumothorax, and mitral valve prolapse. During admission he became drowsy. A CT scan of the brain showed an intracerebral hemorrhage of the left hemisphere. Coagulation tests were normal. Cerebral angiography did not reveal an intracranial aneurysm or other vascular abnormalities.

TABLE 2. Complications During Follow-up in 129 Patients With Marfan Syndrome

	No. of Patients
Surgical correction of extreme aortic dilatation	5
Spontaneous pneumothorax	5
Progression of anterior chest deformity	3
Dissection of ascending aorta	4
Progressive scoliosis	2
Intracerebral hemorrhage	1
Surgical correction of an atrial septum defect II	1

In none of the 826 patients admitted to the departments of neurology or neurosurgery with subarachnoid hemorrhage or intracranial aneurysm was the diagnosis of Marfan syndrome made.

Our review of the literature revealed 10 cases of patients with Marfan syndrome and intracranial aneurysm.[16-25] Eight female and 2 male patients were described, with a median age of 41.3 years.

Discussion

No symptomatic intracranial aneurysm occurred in our population of patients with Marfan syndrome or became clinically overt during the follow-up. In our population of patients with intracranial aneurysm, Marfan syndrome was not diagnosed.

The relationship between Marfan syndrome and intracranial aneurysm, as suggested in the literature,[6-11] is probably based on several case reports of intracranial aneurysm in patients with Marfan syndrome,[16-25] an autopsy report of a young woman with Marfan syndrome,[26] and a family of which several members had intracranial aneurysms and one other member had Marfan syndrome.[27]

Ten cases have been reported of patients with Marfan syndrome and an intracranial aneurysm.[16-25] In all of these the diagnosis of Marfan syndrome was based on clinical manifestations. However, in some patients these manifestations were incompletely mentioned; for example, Higashida et al[21] reported no manifestations at all, and Rose and Pretorius[23] only mentioned a medical history that revealed repair of an ascending aortic aneurysm and replacement of an aortic valve. The diagnosis of Marfan syndrome in some of these patients may be questioned. It is well known that Marfan syndrome can be erroneously diagnosed, especially in patients with homocystinuria[28] or Ehlers-Danlos syndrome type IV.[29]

Ter Berg et al[27] described a family in which seven members presented with intracranial aneurysms and one member with subarachnoid hemorrhage. One other family member was said to have Marfan syndrome, without further details. The patient with Marfan syndrome underwent cerebral angiography, which disclosed no intracranial aneurysm. Thus, this report provides no further evidence for the co-occurrence of intracranial aneurysms and Marfan syndrome.

Stehbens et al[26] examined the cerebral arterial forks of a 33-year-old woman with Marfan syndrome who died of septicemia after cardiac surgery. They found no intracranial aneurysms but described atrophic changes and a small evaginated pouch supposedly associated with early aneurysm formation. No control observations in patients without Marfan syndrome were performed, and on the basis of this single patient they concluded that the development of intracranial aneurysms in patients with and without Marfan syndrome was similar.

In several large series of patients with Marfan syndrome with comprehensive descriptions of the clinical manifestations, the occurrence of intracranial aneurysms is not mentioned.[3,30-32] If there were no intracranial aneurysms at presentation, this does not exclude a future development of intracranial aneurysms. However, during 581 patient observation years no symptomatic intracranial aneurysm developed, while the majority of the known complications of Marfan syndrome did occur. Of course, we cannot exclude the presence of asymptomatic intracranial aneurysms. In autopsy studies unruptured intracranial aneurysms are found in 0.8% to 2.0% of cases.[33-35] Our Marfan patients had an average age of 21.1 years at presentation. We found no evidence of intracranial aneurysms during a total retrospective (2850 years) and prospective follow-up period of 3431 years. The 95% confidence limits of these findings are 0 to 0.001 events per year. In population studies the incidence is approximately 0.001 subarachnoid hemorrhages per year.[14,15] This does not refute any correlation between the two entities but is certainly not suggestive of a strong relation.

At present there is insufficient evidence to postulate an association between Marfan syndrome and intracranial aneurysms. Investigations into a possible pathogenic role of fibrillin deficiency in the development of intracranial aneurysms are not warranted.

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