Increased Prevalence of Cerebrovascular Disease in Hospitalized Patients with Marfan Syndrome

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Background and Purpose: Small studies have suggested that Marfan syndrome is associated with a number of cerebrovascular complications. We sought to determine whether a clinical diagnosis of Marfan syndrome is associated with a higher prevalence of cerebrovascular diseases than the general population by performing a case-control study of hospitalized patients in the Nationwide Inpatient Sample (NIS). *Methods:* Using the 2000-2012 NIS, we performed a case-control study matching cases of Marfan syndrome to controls without such a diagnosis. The prevalence of various cerebrovascular diseases between the 2 groups were compared, and multivariate logistic regression was used to adjust for suspected comorbidities. *Results:* Between 2000 and 2012, there were a total of 13,883 discharges carrying a diagnosis of Marfan syndrome. On univariate analysis, patients with Marfan syndrome were more likely to have a primary or secondary diagnosis of hemorrhagic stroke (0.5% versus 0.3%, odds ratio [OR] = 1.56, 95% confidence interval [CI] = 1.06-2.29, P = 0.02) as well as intracranial hemorrhage (subarachnoid hemorrhage [SAH] and hemorrhagic stroke) (0.3% versus 0.2%, OR = 1.72, 95% CI = 1.05-2.82, P = 0.03). Patients hospitalized with Marfan syndrome were significantly more likely to have carotid dissection (0.3% versus 0.0%, OR = 11.69, 95% CI = 3.60-38.08, P <. 0001) and cerebral aneurysms (0.2% versus 0.1%, OR = 3.67, 95% CI = 1.76-7.68, P = 0.0002). On multivariate analysis adjusted for age, race, and comorbidities, patients with Marfan syndrome had significantly higher odds of ischemic stroke (OR = 1.20, 95% CI = 1.02-1.43, P = 0.03), hemorrhagic stroke (OR = 1.75, 95% CI = 1.18-2.63, P = 0.005), carotid artery dissection (OR = 11.94, 95% CI = 4.23-50.03, P < 0.0001), and cerebral aneurysm (OR = 3.95, 95% CI = 1.95-8.90, P < 0.0001). *Conclusions:* There is a modestly increased prevalence of ischemic stroke, hemorrhagic stroke, and cerebral aneurysms in hospitalized patients with Marfan syndrome when compared with controls. **Key Words:** Marfan syndrome—cerebral aneurysm—carotid dissection—cerebrovascular malformation—carotid aneurysm—vertebral dissection—ischemic stroke—hemorrhagic stroke.
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Introduction

Marfan syndrome is the most common inherited connective tissue disorder, with a reported prevalence of 2-3 per 10,000 individuals.[1] The classical features of Marfan syndrome are aortic root disease, mitral valve prolapse, long bones and joint laxity, arachnodactyly, and ectopia lentis.[2] A number of small studies have suggested that Marfan syndrome is also associated with a wide range of cerebrovascular complications including intracranial and cervical aneurysms, arterial dissections, and ischemic and/ or hemorrhagic strokes.

There have been no large series to address the prevalence of cerebrovascular events requiring hospitalization among patients with Marfan syndrome. We sought to determine whether a clinical diagnosis of Marfan syndrome is indeed associated with higher prevalence of cerebrovascular diseases compared to the general population by assessing ischemic and hemorrhagic stroke, intracranial aneurysm, and arterial dissection, and performing a case-control study of hospitalized patients in the Nationwide Inpatient Sample (NIS).

Methods

Patient Population and Selection

The 2000-2012 NIS of the Healthcare Cost and Utilization Project, sponsored by the Agency for Healthcare Research and Quality (AHRQ, Rockville, MD), was used in our study to collect de-identified administrative and clinical data on US hospital discharges. The NIS is a large administrative database that contains a yearly record of 20% of all discharges (randomly selected) from non-federal hospitals in the United States. Data for roughly 7-8 million hospital discharges are recorded in the NIS annually. Each individual hospitalization is assigned 1 primary discharge diagnosis code and up to 24 distinct secondary diagnoses codes. Similarly, procedural codes for up to 15 distinct types of procedures performed during any individual hospitalization are also recorded. Detailed information on the NIS is available at https://www.hcup-us.ahrq.gov/databases.jsp.

Both adult and pediatric patients with Marfan syndrome were identified using the International Classification of Diseases, Ninth Revision (ICD-9) diagnosis code 759.82. In addition to patients with Marfan syndrome, we selected a random group of controls from the NIS during this same time period. No matching between the Marfan and control groups was performed by design, as we sought to study all relevant demographic and clinical differences between the Marfan and the hospitalized control groups.

Baseline Patient Characteristics

The following baseline demographic characteristics were collected for each patient: age, sex, and race. Patients were divided into 3 age groups: age ≤18, age 19-54, and age ≥55. Stroke risk factors including diabetes mellitus, hypertension, smoking, arrhythmia, and coronary artery disease were collected. ICD-9 codes and Clinical Classifications Software codes corresponding to these diagnoses are summarized in Table 1.

Outcomes

The following primary or secondary diagnoses were compared between groups: acute ischemic stroke, transient ischemic attack, intracranial hemorrhage, subarachnoid

Table 1. *ICD-9 codes*

	ICD-9 code	CCS code
Comorbidity		
Smoking	3051	
Hypertension		98,99
Diabetes		49,50
Arrhythmia		106
Coronary artery disease		101
Complication		
Stroke	433X1, 434X1	
TIA	4358-4369	
ICH	431	
SAH	430	
Carotid dissection	44321	
Vertebral dissection	44324	
Neck aneurysm	44281	
Cerebral aneurysm	4373	
Cerebral vascular malformation	74781	

Abbreviations: CCS, Clinical Classifications Software; ICD-9, International Classification of Diseases, Ninth Revision; ICH, intracranial hemorrhage; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack.

hemorrhage (SAH), carotid dissection, vertebral dissection, neck aneurysm, cerebral aneurysm, and cerebral vascular malformations.

Statistical Analysis

Statistical comparisons of baseline characteristics and clinical diagnoses were made between the Marfan group and the control group. For categorical variables, chi-square test was performed. For continuous variables, Student's t-test was performed. We also performed a multivariate logistic regression analysis to determine if the presence of Marfan syndrome was an independent risk factor for cerebrovascular complications. For this analysis, we adjusted for all baseline comorbidities (Table 1), which were different between groups. Multivariate logistic regression analysis results are reported as odds ratios (OR) and 95% confidence intervals (CI). Discharge weights were not applied to this analysis. For all statistical analyses, we used the Statistical Analysis System-based statistical software package JMP12.0 (www.jmp.com, Cary, NC). Statistical significance is defined as $P < .05$; all P values are 2 tailed.

Results

Baseline Characteristics

Between 2000 and 2012, there were a total of 13,883 discharges carrying a diagnosis of Marfan syndrome. We selected an equal number of random controls for a total of 27,886 patients.