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Epidemiological Profile of Marfan Syndrome in a General Population: A National Database Study

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Abstract

Objective: To explore the current epidemiological profile of Marfan syndrome in a general population.

Patients and Methods: Patients who had received a diagnosis of Marfan syndrome were identified from the Taiwan National Health Insurance database records from January 1, 2000, through December 31, 2012 (average population size, 22,765,535). Cardiovascular events and interventions were identified by using the respective *International Classification of Diseases* codes.

Results: We identified 2329 patients (58% men) with Marfan syndrome. The overall prevalence was 10.2 (95% CI, 9.8-10.7) per 100,000 individuals, with peaks at the age of 15 to 19, 10 to 14, and 20 to 24 years. The minimal birth incidence of 23.3 (95% CI, 21.7-23.3) per 100,000 individuals was estimated in those aged 20 to 29 years. The average annual mortality was 0.23% (69 deaths), mostly owing to cardiac causes (including dissection and sudden death in 40 patients, 58%). Aortic dissection occurred in 226 patients (10%; 61% men) at a mean age of 36.6±10.7 years. The probability of freedom from dissection was 99%, 80%, and 66% at the age of 20, 40, and 50 years, respectively. Of the 69 deaths and 226 dissections during the follow-up period, more than half of the cases occurred before the age of 40 years. Cardiovascular intervention was performed in 360 patients, with early mortality being higher in the emergent operation group (8%) than in the elective group (0%).

Conclusion: From this national cohort study, the minimal birth incidence was 23.3 per 100,000 individuals, that is, possibly 1 patient with Marfan syndrome per 4286 people. Despite medical advances, aortic dissection still occurs in about one-tenth of the patients and carries a high mortality risk. Early diagnosis and timely medical interventions are warranted.

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Marfan syndrome is a multisystem connective tissue disorder that may lead to progressive or even fatal aortic root dilation. It occurs worldwide, with no predilection for either sex. The prevalence of Marfan syndrome is often estimated to be 1 per 5000 to 10,000 individuals, and the incidence is estimated to be 2 to 3 per 10,000 individuals, although these estimates depend on the recognition of all affected and genetically predisposed individuals.[1-5] In a UK cohort of 441,000, the incidence was estimated to be 1 per 9802 individuals and a minimal birth incidence of 1 per 14,217 individuals.[5] The factors that may underestimate the prevalence or incidence are as follows: (1) the phenotype becomes more apparent only with increasing age, (2) approximately 25% of the cases are sporadic owing to de novo sequence variations, without a family history of Marfan syndrome, and (3) no rapid and efficient molecular diagnostic test exists. Early reports suggest that because of the high incidence of aortic root dilation and the associated risk of life-threatening aortic dissection, life span is often shortened.[1] However, the life expectancy has increased substantially over the past 3 decades because of advanced applications of genetic screening, medical management, and surgical management.[3-8]

The population of Taiwan is approximately 23 million, with 21% being the pediatric population (younger than 18 years). The National Health Insurance (NHI) Program was implemented in 1995 and has covered more than 99% of the general population. The health care system in Taiwan is regarded as sound, and the child health index is similar to that in the United States.[9] We hypothesized that the number of patients with Marfan syndrome and the related cardiovascular complications in Taiwan, a country with fully covered and easily accessible medical care, would adequately reflect the prevalence

and cardiovascular risk in patients with Marfan syndrome. Therefore, this study explored the current epidemiological profile of Marfan syndrome by using our national database spanning 13 years.

PATIENTS AND METHODS

National Health Insurance Database and Patient Identification

The institutional research board of National Taiwan University Hospital approved this study and waived the need for informed consent. All health care records logged from January 1, 2000, through December 31, 2012, were retrieved from the complete computerized database of the NHI. The average population size was 22,765,535. Patients who had received a diagnosis of Marfan syndrome (code 759.82) according to the criteria listed in the *International Classification of Diseases, Ninth Revision, Clinical Modification* were selected. Each health record had a scrambled identification number and contained information such as the patient's date of birth, date of hospital visit, sex, type of visit (admission or outpatient department visit), diagnosis and treatment codes, and reimbursement fees. To estimate the prevalence, we defined patients as anyone admitted to a hospital with the diagnosis of Marfan syndrome or those who visited the outpatient department with the diagnosis of Marfan syndrome at least thrice. The overall prevalence and age-specific prevalence (per 100,000 individuals) were calculated from the sex-specific population sizes recorded from 2000 through 2012 by 5-year age categories.

Definition of Aortic Dissection and Interventions

Identified patients were tracked for any complications or interventions (defined subsequently) until December 31, 2012. The occurrence of aortic dissection was defined as a listing of any of the following disease codes for first, second, or third diagnosis: 441.0 (dissection of aorta), 441.1 (thoracic aneurysm, ruptured), 441.3 (abdominal aneurysm, ruptured), or 441.5 (aortic aneurysm of unspecified site, ruptured), and 441.6 (thoracoabdominal aneurysm, ruptured). Cardiovascular intervention was defined by any of the following *International Classification of Diseases* codes: cardiac operation: 351, 352, 353, 359, 360, 361, 363, 374, 375, 377, and 383; vascular operation: 384, 392, and 394; and endovascular repair: 397. Early mortality was defined as the event of death occurring at discharge.

Statistical Analyses

We used the Statistical Package for Social Sciences statistical software (SPSS, version 15.0, SPSS Inc) for analysis. The independent *t* test was used to compare means between continuous variables, and the χ^2 test was used to analyze associations between categorical variables. The overall prevalence and age-specific prevalence (5-year age categories) were calculated from the sex-specific population sizes recorded from 2000 through 2012, which were adopted from the Statistical Yearbook of the Interior, Department of Statistics, Ministry of the Interior. Kaplan-Meier analysis was used for time-dependent variables to determine the probability of freedom from dissection, reintervention, and mortality. Multivariate analyses by stepwise logistic regression models were used to identify the possible risk factors of mortality. Variables included age group, sex, dissection, emergent treatment, interventions, and reintervention. Those with $P<.05$ were included for analysis, and those with $P>.1$ were excluded. A *P* value of less than .05 was considered statistically significant.

RESULTS

Prevalence and Survival

In the study period from 2000 to 2012, 2329 patients (58% men) with Marfan syndrome were identified. The average prevalence was 10.2 (95% CI, 9.8-10.7) per 100,000 individuals, that is, 1 per 9804 people in the general population. The age-specific prevalence is illustrated in Figure 1. The highest peak was noted in the age range of 15 to 19 years, followed by the ranges 10 to 14 and 20 to 24 years. The birth incidence was then estimated from the point prevalence of affected individuals who would have been/be aged between 20 and 29 years on the prevalence day in comparison with the total number of individuals aged between 20 and 29 years on that same day. There were 784 patients with Marfan syndrome, and the minimal birth incidence was 23.3 (95% CI, 21.7-23.3) per 100,000 individuals, that