Do Familial Aortic Dissections Tend to Occur at the Same Age?

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Background. Prediction of the age at aortic dissection for family members of aortic dissection patients would enhance early detection and clinical management. We sought to determine whether these dissections tend to cluster by age in family members of the dissection patients.

Methods. Ages at dissection were examined, including 51 sporadic dissectors (one dissection in family) and 39 familial dissectors (two or more dissections in family) from 16 families. Differences between sporadic and familial dissectors and relationships between ages at dissection in family members were analyzed by linear regression and clustering analysis.

Results. Age at dissection was significantly younger in familial versus sporadic dissectors (54.1 ± 15.2 years versus 63.1±12.4 years, $p = 0.002$). Regression analysis of pairs of family member ages at dissection found a moderately close linear fit ($R^2 = 0.35$). Cluster analysis indicated that age at onset of family dissectors increases

as age of proband dissector increases. More than 50% of familial dissections occurred within 10 years of the median onset age for any given age decade. For familial dissectors with onset age of 30 to 49 years, 71% of other family member dissections also occurred at age 30 to 49 years, and no dissections occurred above the age of 63 years. For familial dissectors with onset age of 60 to 79 years, 80% of other family member dissections occurred beyond the age of 50 years.

Conclusions. Familial dissections occur earlier than sporadic dissections. Dissections cluster by age in families, and age at onset can predict the age of other dissectors. This finding argues for consideration of prophylactic resection of an aneurysm in family members approaching the age at onset of prior thoracic aortic dissection.

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Thoracic aortic dissection (TAD) is a deadly disease, which underscores the importance of early diagnosis and timely application of surgical therapy. As most patients with aortic dissection are asymptomatic before onset, predictive markers for looming dissection and potential prophylactic treatment are desirable [1]. In recent years, several clinical markers have been correlated with increased risk of thoracic aortic aneurysm and TAD [2–9].

Our group [3] and Milewicz and colleagues [10] described the importance of family history in nonsyndromic cases of thoracic aortic disease [2–4, 11, 12]. We also found that familial aortic dissection had higher aortic growth rates than both sporadic and syndromic aortic dissections [4]. A positive family history is becoming an

important screening marker for thoracic aortic aneurysm and dissection. Next-generation screening genetic studies promise to enhance the role of familial patterns in the treatment of thoracic aortic disease [12–19]. At present, however, the specific prognostic value of family history of TAD events has not been extensively studied [20–24].

In this study, we shift our focus toward insights made possible from family history information alone. We examine specific characteristics of families with two or more dissectors and compare the characteristics of familial TAD with sporadic TAD. Through detailed collection of family histories of patients with TAD, we assess the patterns of inheritance and look for age clustering. We anticipate that finding clustering may provide insights into the dissection risk for family members of patients with TAD.

Material and Methods

Patients

Through an institutional registry containing all dissection patients treated by the Aortic Institute at Yale from 1990

to May 2014, we isolated 298 TAD patients who were still alive. Concerted contact efforts were made for all these patients and their families. Familial information permitting construction of accurate, detailed family histories was available for 90 patients.

The study was approved by the Human Investigations Committee of Yale University. The need for written consent was waived, and patients gave verbal consent for participation in the study at the time of phone interviews to collect family history information.

Classification of Family History of TAD

Proband patients were selected based on the occurrence of aortic dissection in immediate family members (first- or second-degree relatives). Probands were noted as sporadic dissectors and assigned negative family history status if they had no first- or second-degree relatives who also had a confirmed TAD. For the purposes of this study, relatives with non-dissecting aneurysms, stroke, or sudden death of unknown etiology were considered negative. Probands were classified as familial dissectors and assigned positive family history status if at least one first- or second-degree relative had a confirmed TAD. In this study, no special distinctions were made for "syndromic" dissections such as Marfan or Ehlers-Danlos, as it is becoming clear that many if not all familial dissections have a strong genetic component, even if the precise genetic locus is unknown. Sample pedigrees for a sporadic and familial proband are shown in Figure 1.

Of the 90 patients, 51 patients were sporadic dissectors with no family history, and 39 patients were dissectors with confirmed family history of aortic disease.

Clustering Analysis of Familial Age at Dissection and Statistical Analysis

Age at onset of sporadic and familial dissections was analyzed and compared. Linear regression was used to further investigate the relationship of age at dissection in familial cases. Box-and-whisker plots were used to examine relationships between ages at dissection of individual probands with ages at dissection of family members.

Data are expressed as mean ± SD or as percentages. Comparison of means was performed using Student's t test, whereas comparison of proportions was performed with Pearson's χ^2 test. Methods for determination of age clustering in familial dissectors include comparison of average difference in age at dissection, linear regression, and cluster analysis.
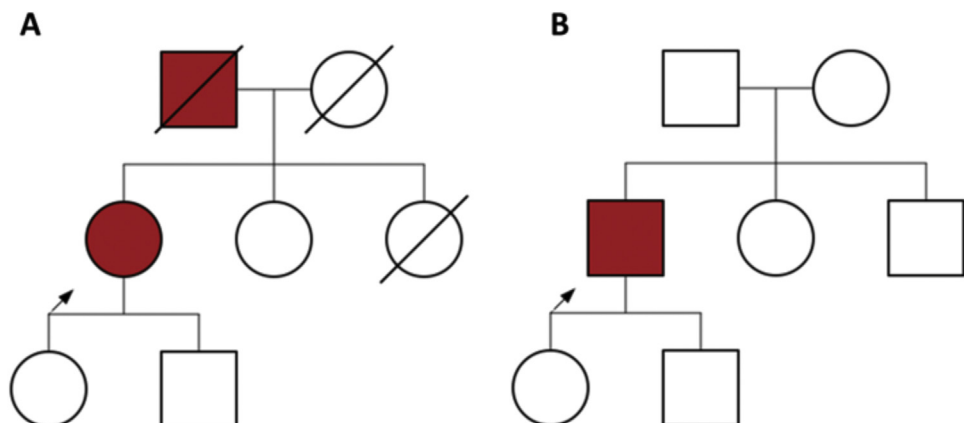
Results

Patient Profile

Of the patients in this study, 39 of the 90 dissectors (43%) reported family history of aortic disease. The 90 respondents had, in total, 483 first-degree relatives, and among those relatives, 39 occurrences of TAD were observed (8.0%).

Ninety patients had sufficient family history data and were included in this study. Average age at diagnosis was 59.1 ± 14.3 years (range, 26 to 84) and 57 (63%) were male. Sporadic dissection occurred in 51 patients, and 39 patients had a family history of aortic dissection. The 39 familial dissections occurred in 16 distinct families. The number of dissectors per family ranged from two to five. Of the 39 patients with familial aortic dissection, reliable data were available for 32 patients (82%). Of these 32 patients, 23 (72%) had a type A aortic dissection and 9 patients (28%) had a type B dissection. Of the 16 families, seven have dissections all in the same location, five have family members with dissections in different locations, and four are unknown (only one family member reporting). Syndromic dissection occurred in 14 patients from six families. The frequency distribution of aortic dissections by age, familial and sporadic, is shown in Figure 2.

Comparison of Sporadic and Familial Dissectors

Mean age at dissection for familial patients (54.1 ± 15.2 years) was significantly less than for sporadic patients (63.1 ± 12.4 years; $p = 0.002$). Comparison of the mean difference in age at dissection between two randomly selected sporadic dissectors (14.0 ± 10) with mean difference in age at dissection between two dissectors of the same family (9.9 ± 7.0) revealed that dissections in the

Fig 1. Sample pedigrees for (A) familial aortic dissection, and (B) sporadic aortic dissection. Red squares and circle indicate patients or family members with aortic dissection. Arrow indicates index patient (proband).