Canadian Journal of Cardiology 32 (2016) 86–99

Review

The Expanding Clinical Spectrum of Extracardiovascular and Cardiovascular Manifestations of Heritable Thoracic Aortic Aneurysm and Dissection

Timothy J. Bradley, MBChB,[a] Sarah C. Bowdin, BM, MSc,[a,b] Chantal F.J. Morel, BSc, MD,[c] and Reed E. Pyeritz, MD, PhD[d]

[a] *Division of Cardiology, Department of Paediatrics, The Labatt Family Heart Centre, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada*

[b] *Division of Clinical and Metabolic Genetics, Department of Paediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada*

[c] *Fred A. Litwin Family Center in Genetic Medicine, Department of Medicine, University Health Network and Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada*

[d] *Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA*

ABSTRACT

More than 30 heritable conditions are associated with thoracic aortic aneurysm and dissection (TAAD). Heritable syndromic conditions, such as Marfan syndrome, Loeys-Dietz syndrome, and vascular Ehlers-Danlos syndrome, have somewhat overlapping systemic features, but careful clinical assessment usually enables a diagnosis that can be validated with genetic testing. Nonsyndromic FTAAD can also occur and in 20%-25% of these probands mutations exist in genes that encode elements of the extracellular matrix, signalling pathways (especially involving transforming growth factor-β), and vascular smooth muscle cytoskeletal and contractile processes. Affected individuals with either a syndromic presentation or isolated TAAD can have mutations in the same gene. In this review we focus on the genes currently known to have causal mutations for syndromic and isolated FTAAD and outline the range of associated extracardiovascular and cardiovascular manifestations with each.

RÉSUMÉ

Plus de 30 affections héréditaires sont associées à l'anévrisme et à la dissection de l'aorte thoracique (TAAD : *thoracic aortic aneurysm and dissection*). Les affections héréditaires syndromiques, comme le syndrome de Marfan, le syndrome de Loeys-Dietz et la forme vasculaire du syndrome d'Ehlers-Danlos, présentent des caractéristiques systémiques qui se recoupent quelque peu, mais une évaluation clinique consciencieuse permet habituellement de poser un diagnostic qui peut être validé par dépistage génétique. La forme familiale non syndromique de TAAD peut également apparaître, et 20 % à 25 % des mutations chez les proposants existent dans les gènes qui encodent les éléments de la matrice extracellulaire, les voies de signalisation (impliquant particulièrement le facteur de croissance transformant β [TGF-β : *transforming growth factor* β]) et les processus cytosquelettiques et contractiles des muscles lisses vasculaires. Les individus qui présentent soit le tableau clinique d'un syndrome ou un TAAD isolé peuvent avoir des mutations dans le même gène. Dans cette revue, nous nous concentrons sur les gènes actuellement connus comme étant porteurs de mutations causales de TAAD familial syndromique et isolé, et exposons les grandes lignes des diverses manifestations cardiovasculaires et extracardiovasculaires associées à chacune.

More than 120 years since Marfan's original report,[1] > 30 heritable conditions have been found that involve aortic and arterial aneurysms,[2] and the list continues to grow. Consequently a physician today faced with an individual with thoracic aortic aneurysm and dissection (TAAD), especially one with an affected relative, has a large clinical spectrum of conditions to consider. Syndromic conditions such as Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), and vascular Ehlers-Danlos syndrome (vEDS), that all share a predisposition to TAAD, can also have somewhat overlapping systemic features. The diagnosis of these conditions usually is reliant on an assessment of the individual and their family history by a clinical geneticist, and more recently, confirmation with genetic testing of a mutation in the respective genes, *FBN1* (MFS), *TGFBR1* and *TBFBR2* (LDS), and *COL3A1* (vEDS). In the past 20 years, isolated familial TAAD (FTAAD) has

Received for publication October 26, 2015. Accepted November 9, 2015.

Corresponding author: Dr Timothy J. Bradley, The Labatt Family Heart Centre, The Hospital for Sick Children, 555 University Ave, Toronto, Ontario M5G 1X8, Canada. Tel.: +1-416-813-7610; fax: +1-416-813-7547.

E-mail: timothy.bradley@sickkids.ca

See page 95 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2015.11.007

also been described and in 20%-25% of these families mutations are now identifiable.[3] However, the situation is complicated because affected individuals with either a syndromic or isolated presentation can have mutations in the same gene, which makes it difficult to predict the complications that might occur. Many of these conditions also show significant intrafamilial variability, meaning that it is potentially possible to detect syndromic manifestations in some family members although others within the same family appear to have isolated aortic involvement. In addition, with the advent of multigene panel testing for TAAD, the milder end of the phenotypic spectrum has now become apparent for some of these more recently described syndromes.

In this review we focus on the genes known to cause TAAD and outline the range of extracardiovascular and cardiovascular manifestations associated with these conditions. The conditions are presented according to whether the gene involves extracellular matrix (ECM) proteins, the transforming growth factor-β (TGF-β) signalling pathway, vascular smooth muscle cytoskeleton, or contractile elements, or other signalling pathways. Conditions with significant overlap in extracardiovascular features with syndromic TAAD are also described to emphasize the expanding spectrum of differential diagnoses.

ECM Protein Genes

The extracardiovascular and cardiovascular manifestations of the conditions associated with ECM protein genes below are listed in Table 1.

FBN1

MFS. In 1896, Antoine Bernard-Jean Marfan described a 5-year-old girl with a long narrow skull (dolichocephaly), tall stature with disproportionately long thin limbs (dolichostenomelia), and long, thin fingers and toes (arachnodactyly).[1] MFS has evolved since as a highly variable, multisystem disorder that affects many organ systems. In 1943, TAAD was first noted in patients with MFS.[4,5] Autosomal dominance was described in 1931,[6] and the first causal mutation in *FBN1*, encoding fibrillin-1, a glycoprotein component of the extracellular microfibril, was reported in 1991.[7] MFS is the most common connective tissue disorder with an estimated prevalence of approximately 1 per 3000-5000 population.[8]

Extracardiovascular manifestations. Victor McKusick catalogued the clinical features of MFS in 1955,[9] and a succession of diagnostic criteria evolved to the Revised Ghent Nosology.[10] The diagnostic criteria now put more weight on the cardinal clinical features of TAAD, ectopia lentis, and the presence of a pathogenic *FBN1* mutation. The other clinical features of MFS considered most important have now been combined into a systemic score with a total of 20 points.[10] In the absence of a positive family history or features suggestive of an alternative diagnosis, the presence of 2 of these cardinal features or alternatively aortic involvement with a positive systemic score is sufficient for the unequivocal diagnosis. With a known family history of MFS, the presence of either ectopia lentis, or a positive systemic score, or significant aortic root involvement (z score ≥ 2 if older than 20 years or ≥ 3 if younger than 20 years) is sufficient for the diagnosis.

Aortopathy. Aortic involvement in MFS is most frequently aortic root aneurysm that might extend into the ascending aorta and a predisposition to type A aortic dissection.[11] Aortic dissection or the need for prophylactic aortic root replacement tend not to occur until the third or fourth decade of life in most individuals with MFS, but can occur during adolescence. Descending thoracic aorta aneurysm and type B aortic dissection are less common, but the frequency appears to be increasing in MFS because of improved survival.[12,13]

Arterial involvement. Main pulmonary artery dilation is frequent in MFS,[14-17] but rarely requires surgical intervention because dissection is rare.[18] Arterial aneurysms in MFS do not appear to occur at any increased level beyond the general population risk. However, increased arterial and aortic tortuosity is evident in MFS and is associated with worse cardiovascular outcomes.[19,20]

Valvulopathy. Mitral valve prolapse (MVP) is very common in MFS and might progress to severe mitral regurgitation, especially in women, by adolescence.[21] Flail mitral leaflet secondary to a ruptured chord and increased left ventricular end-systolic dimension are independent predictors for progression of mitral valve regurgitation.[22] Tricuspid valve prolapse with or without regurgitation is less common and less likely to produce any complications. The exception is with the most severe end of the MFS spectrum, previously considered as the "neonatal" or "infantile" form.[23,24] In this setting, early-onset severe mitral and tricuspid regurgitation can cause refractory heart failure. Often, in conjunction with myocardial dysfunction, congenital contractures, chest deformity, other severe musculoskeletal phenotypic features, and "infantile pulmonary emphysema"; this is fatal in the first year, even after valvular repair. Aortic regurgitation usually progresses with aneurysmal dilatation of the aortic root.

Myocardial involvement. "Arachnodactyly heart" was first reported in 1959.[25] However, myocardial involvement in adult MFS continues to be mostly considered a secondary phenomenon due to valvular insufficiency and ventricular volume overload.[26] Myocardial dysfunction in children with severe MFS is well described,[23,24] but again this is in the setting of severe valvular regurgitation and ventricular volume overload in neonatal life and potentially during fetal development. Mild impairment of myocardial function independent of valvular and aortic involvement likely exists in some individuals with MFS and ventricular functional assessment should be part of routine long-term follow-up.[27-39] Additionally, a relationship between a specific genotype in MFS with a nonmissense *FBN1* mutation and left ventricular dilatation has been recently reported.[40] Important ventricular arrhythmia can also occur in MFS with or without significant valvulopathy.[41,42]

Isolated FTAAD-*FBN1*. *FBN1* mutations have also been described in isolated FTAAD.[43]

MASS phenotype. *FBN1* mutations have been found occasionally in MASS phenotype. First described in 1989,[44] MASS phenotype required at least 2, but preferably 3, of the following: myopia, MVP, borderline aortic root