Canadian Journal of Cardiology 32 (2016) 60–65

Review

Screening Children for Familial Aortopathies: Tread With Caution

Julie Richer, MD,[a] and Anne-Marie Laberge, MD, MPH, PhD[b]

[a] Department of Medical Genetics, Children's Hospital of Eastern Ontario, Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada

[b] Medical Genetics, Department of Pediatrics, and Research Center, CHU Sainte-Justine; and Department of Pediatrics, Université de Montréal; and Department of Medicine, Montreal Heart Institute, Montreal, Quebec, Canada

ABSTRACT

The knowledge surrounding the genetic etiologies of familial aortopathies and familial thoracic aortic aneurysms and dissections has greatly expanded over the past few years. However, despite these advances, the underlying molecular etiology remains unidentified in most families with nonsyndromic familial aortopathies, and in a subset of families with syndromic aortopathies. In these families we cannot offer a genetic test to establish which family members are at risk. Although the general consensus has been to clinically follow all at-risk family members on the basis of family history, it remains unclear at the age at which to initiate clinical surveillance and the frequency which to screen asymptomatic relatives, whether or not a genetic etiology has been established in the family. These questions are particularly troublesome in a pediatric context where the risks of screening are potentially higher and the likelihood that such screening will provide immediate benefits is often lower than in adults. In this report we aim to: (1) provide clinicians with a framework within which to evaluate risks and benefits of screening asymptomatic pediatric

RÉSUMÉ

Au cours des dernières années, d'importants progrès ont été réalisés au sujet de l'étiologie génétique des aortopathies familiales ainsi que des anévrismes aortiques thoraciques et des dissections aortiques. En dépit de cela toutefois, la cause moléculaire sous-jacente de la maladie demeure inconnue pour la plupart des familles atteintes d'aortopathie familiale non syndromique et pour un sous-groupe de familles atteintes d'aortopathie familiale syndromique. La communauté médicale ne dispose donc, à l'heure actuelle, d'aucun outil de dépistage génétique permettant de déterminer qui, dans ces familles, est exposé à un risque. Le consensus actuel dicte d'offrir un suivi médical à toutes les personnes que l'on juge exposées à un risque en fonction de leurs antécédents familiaux, mais on ne sait pas encore à quel âge il faut entreprendre un tel suivi ni à quelle fréquence il faut l'offrir aux personnes asymptomatiques, que l'étiologie génétique de la maladie ait été établie ou non. Ces questions se posent tout particulièrement dans le contexte de la médecine pédiatrique où les risques associés au dépistage sont souvent plus élevés et où les bienfaits

Familial aortopathies, or familial thoracic aortic aneurysms and dissections (TAADs), are defined as the presence of a progressive enlargement of the ascending thoracic aorta involving the sinuses of Valsalva, the ascending aorta, or both, in an individual with a family history of TAAD.[1] Nonsyndromic TAAD imply that syndromic causes of familial TAAD (FTAAD), such as Marfan syndrome, Ehlers Danlos syndrome, vascular type, and Loeys-Dietz syndrome (LDS) were excluded. A family history of TAAD is present in approximately 20% of individuals with nonsyndromic TAAD.[2]

The Landscape

In familial aortopathies, current practice is to perform imaging, usually an echocardiogram, in first-degree relatives to investigate for aortic dilation, and to repeat this imaging at regular intervals to detect aortic dilatation as early as possible.[3] In families with a genetic diagnosis confirmed with genetic testing, at-risk family members might be tested for the familial mutation to determine whether they are at risk of developing an aortopathy. If they have inherited the familial mutation, monitoring at regular intervals is justified. If they have not inherited the familial mutation, they are not considered at increased risk compared with the general population and monitoring is not indicated. In families without a molecular diagnosis, all individuals considered at risk on the basis of family history will require monitoring. Because current knowledge suggests that most familial aortopathies are transmitted following an autosomal dominant pattern, then we assume that 50% of individuals in families without a molecular diagnosis will be monitored unnecessarily, because they have not inherited the genetic predisposition and will in fact never develop the disease. Without a molecular diagnosis, we have no way of telling them apart from their relatives who have inherited the predisposition but have yet to display signs on imaging. Adult relatives are candidates for genetic testing and/or imaging as soon as they are identified as being at risk. For children, screening for familial aortopathy with genetic tests and/or imaging raises additional questions.

Received for publication September 6, 2015. Accepted October 7, 2015.

Corresponding author: Dr Julie Richer, Children's Hospital of Eastern Ontario (CHEO), 401 Smyth Rd, Ottawa, Ontario K1H 8L1, Canada. Tel.: +1-613-737-7600, ext 3496.

E-mail: juricher@cheo.on.ca

See page 65 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2015.10.005

patients for a family history of thoracic aortic aneurysms and dissections; and (2) provide a potential approach for patients (a) in whose family a disease-causing mutation has been identified, (b) patients in whose family the proband is syndromic, but does not have an identified disease-causing mutation, and (c) patients in whose family the proband is nonsyndromic and does not have an identified disease-causing mutation.

immédiats d'un tel dépistage sont moins évidents que chez l'adulte. Dans le présent rapport, nous désirons 1) fournir aux médecins un cadre leur permettant d'évaluer les bienfaits et les risques associés au dépistage d'une aortopathie familiale (et du risque de présenter un anévrisme aortique thoracique ou d'être victime d'une dissection aortique) chez des enfants asymptomatiques et 2) fournir une approche de traitement possible chez les patients a) où l'aortopathie est associée à une mutation génétique familiale, b) chez ceux où l'aortopathie est syndromique, mais pour laquelle aucune mutation génétique n'a été identifiée et c) chez ceux où l'aortopathie est non syndromique et pour laquelle aucune mutation génétique n'a été identifiée.

The American Society of Human Genetics has recently updated their position statement on genetic testing in children and adolescents.[4] In the case of predictive testing, they recommend that testing be deferred until adulthood unless there is a clinical intervention appropriate in childhood, or at least deferred until the child is old enough to participate in decision-making in a relatively mature manner.

In this report we discuss issues that apply to children assessed and/or diagnosed solely on the basis of family history after a diagnosis in an adult relative, including families for whom no clear pathogenic mutation has been identified. The issues raised herein do not necessarily apply to children who are the proband in their own family and for whom a clear pathogenic mutation has been identified, because they are already clinically symptomatic and it is reasonable to believe that such children might be more severely affected.

Genetics of familial aortopathies

The understanding of the genetic basis of familial aortopathies has greatly increased over the past 20 years. Although the detection rate of molecular testing for familial aortopathies varies according to the specific study quoted,[5-8] it remains poor at approximately 20%. This means that in approximately 80% of families with a familial aortopathy, we will not be able to use molecular testing to predict which family members are at risk for the disease.

Familial aortopathies can be divided into syndromic and nonsyndromic causes. The mutation detection rate is higher in syndromic aortopathies than in nonsyndromic aortopathies, reaching 70%-90% for individuals with a clinical diagnosis of Marfan syndrome,[9] which means fewer families will be left without a molecular diagnosis to enable family screening. In families without a molecular diagnosis, patients with syndromic aortopathies might also present nonaortic features, which might assist in identification of individuals who are affected and therefore at risk of aortopathy in the family. For example, individuals with Marfan syndrome often have pectus, scoliosis, or other skeletal features. Ectopia lentis is present in approximately 60% of cases. Individuals with LDS typically have arterial tortuosity; hypertelorism and a bifid uvula are also significantly more common in LDS.

Variability: interfamilial, intrafamilial, and sexual dimorphism

It is now being increasingly recognized that even in families with syndromic aortopathies, there can be significant intrafamilial variability not only with regard to the aortopathy itself (severity, age of onset), but also with regard to other phenotypic manifestations.[10-12] In other words, the presence of associated features might be suggestive of having inherited the condition and therefore also the predisposition to aortopathy, but the absence of associated features does not rule out this risk. As in syndromic aortopathies, substantial intrafamilial variability can be observed in families with nonsyndromic aortopathies.

To further complicate the clinical picture, women often have a lower lifetime risk of aortopathy and often develop such aortopathy at a later age than men, a phenomenon referred to as sexual dimorphism.[13] Such sexual dimorphism has been documented for bicuspid aortic valve with aortopathy, FTAAD, and TAAD at an age younger than 50 years. This phenomenon can therefore make risk interpretation even more difficult for a teenage boy who has a maternal grandfather with an aortopathy, but whose 40-year-old mother still has a normal echocardiogram.

Finally, the aortic diameter at dissection also appears to vary widely between families. Therefore, there must be other factors, besides only the aortic diameter, that significantly contribute to aortic dissection.

Remaining pitfalls even with genetic testing

Predictive genetic testing does not necessarily simplify matters. In a family with a form of aortopathy that can present before adulthood, clinical intervention is appropriate in childhood in a symptomatic child.[4] When genetic testing reveals the presence of a clear pathogenic mutation in a known gene in an asymptomatic child, there are still questions around the age at which screening for aortic dilatation should be performed for this child, how often imaging should be repeated if initial imaging is normal, and whether (and when) to start preventive treatment in children with a known mutation and normal imaging.

Genetic testing might identify different types of variants in the genes analyzed (Table 1). Variants of unknown significance (VUS) are regularly identified in performance of genetic testing. Recent studies have shown a rate of VUS of approximately 18% in individuals with syndromic aortopathies and 21% in unselected adults with TAAD.[5,7] To be prudent, clinicians will often follow a proband with a VUS in a known aortopathy gene as they would someone with a pathogenic mutation in that same gene, while awaiting further knowledge on the variant and its significance. Testing the proband's parents and/or other affected family members for the VUS identified in the proband can in some cases help reclassify a