



Common presentation of rare diseases: Aortic aneurysms & valves

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ABSTRACT

The concept “*common presentation of rare diseases*” implies that rare diseases are masked by common phenotypic manifestations. This concept applies to both aneurysmal and valvular diseases that can be syndromic and non-syndromic. Syndromic disorders include genetic connective tissue diseases and chromosomal disorders that are diagnosed independently from the aneurysm or valve disease. Non-syndromic diseases, on the other hand, are defined by the presence of aneurysm or valve disease or both.

The reasons for suspecting these rare diseases include young age, the absence of risk factors, a positive family history for aortic or valvular disease/event, and extra-cardiovascular traits for syndromes. The probands should receive genetic counseling, genetic testing [single gene in case of precise phenotyping addressing the gene to be tested, or multigene panels, in case of diseases with genetic heterogeneity], post-test counseling, clinical family screening and cascade genetic testing in relatives after the identification of a causative mutation. Segregation studies are essential in case of novel mutations, in particular non-truncation predicting variants.

Clinical family screening of syndromic diseases is facilitated by the evaluation of non-cardiovascular traits; this supports early diagnosis and geno-phenotype correlation. Vice versa, family screening studies in non-syndromic aneurysmal and valvular diseases exclusively relies on CV imaging screening of relatives. In this context, conditions such as BAV and related aortopathy are easy to diagnose because BAV is present at birth while aortopathy usually develops during the life course.

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1. Introduction

The concept “*common presentation of rare diseases*” implies that the diagnosis, as described by the phenotype, refers to a relatively common condition (e.g. aortic aneurysm) but the causes can either be “common” (e.g. hypertension and atherosclerosis) or rare, genetic (typically connective heritable diseases) [1] and non-genetic (e.g. Takayasu's arteritis) [2]. Therefore, cardiologists faced with a patient affected by thoracic aortic aneurysm (TAA), should consider the possibility that, even when apparently isolated or unique in the family, TAA may have a rare genetic or non-genetic cause. This possibility is by itself sufficient to consider a genetic workup, including clinical and molecular (genetic testing) evaluation, for the proband and the family. The major aims of

genetic family studies are the precise diagnosis, tailored monitoring programs and prevention of life-threatening vascular events [3].

The same concepts apply to valve diseases that are common in the general population and frequently acquired (rheumatic, endocarditis, and degenerative), but which can occasionally represent the unique or major clinical manifestation of a rare genetic disease [4]. Cardiac valves are frequently involved in connective tissue diseases with aortic aneurysm: e.g. in newborns and children with Marfan syndrome, mitral valve disease can be the first and most severe manifestation requiring surgery in pediatric age [5]. Rare diseases affecting tricuspid valves (Ebstein anomaly) [6] or pulmonary valves in syndromes such as Noonan syndrome [7], or aortic valve in Turner syndrome [8] are all examples of rare genetic diseases in which cardiac valve diseases are either the main traits of the disease or one of the multiple disease manifestations.

Diagnostic criteria for aneurysmal and valve diseases are based on multimodality imaging that provides detailed information of morphology and function of the cardiovascular system [9–11]. This review addresses the diagnostic workup and clinical management of rare genetic aneurysmal and valvular diseases, both as isolated traits or as part of syndromic conditions, and highlights the role of deep phenotyping and family studies as useful tools for early diagnosis and prevention of life-threatening vascular events.

Abbreviations: TAA, Thoracic aortic aneurysm; TAAD, Thoracic aortic aneurysm and dissection; AAA, Abdominal aortic aneurysm; BAV, Bicuspid aortic valve; MVD, Mitral valve disease; MVP, Mitral valve prolapse; TV, Tricuspid valve; MFS, Marfan syndrome; LDS, Loays–Dietz syndrome; EDS, Ehlers–Danlos syndrome; ATS, Arterial tortuosity syndrome; SGS, Shprintzen–Goldberg syndrome; NS, Noonan syndrome; EL, Ectopia lentis; AR, Aortic root; ARD, Aortic root dilation; ASD, Atrial septal defect; 2D-TTE, 2D-trans thoracic echocardiogram; NGS, Next generation sequencing; CT, Computed tomography.

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2. Rare aneurysmal diseases (Suppl. Table 1)

Genetic aneurysmal diseases can be grouped into syndromic (chromosomal and single-gene diseases) and non-syndromic forms [12–13]. Syndromic aneurysmal diseases are characterized by the presence of phenotypic traits in multiple systems (skeletal, ocular, respiratory, neuromuscular, and integumentary). They include diseases in which the presence of aneurysms does not influence the diagnosis (e.g. Turner syndrome) [8] and in which the aneurysm is a major phenotypic trait and diagnostic contributor (e.g. MFS, LDS, EDS, and SGS) [12,13]. The inheritance is autosomal dominant in the majority of cases, with many *de novo* cases (up to 25–30% of cases in MFS and even higher in LDS).

Non-syndromic aneurysms encompass diseases caused by mutations in the same genes that cause syndromes or in genes whose defects cause only (or mainly) aneurysms [12–14]. Examples of these latter are genes coding for structural or regulatory components of the vascular smooth muscle cells (vSMC) [14] (Suppl. Table 1). Isolated TAA/TAAD is less common than abdominal aortic aneurysm (AAA) [15,16]. The former is more likely to be caused by genetic defects while the latter frequently results from a multifactorial origin. Arteries other than aorta (cerebral, abdominal, and limb) can be involved in aneurysmal diseases and should be systematically investigated [17].

In syndromic aneurysmal diseases, the extra-aortic traits can be present since early childhood and their identification may facilitate the diagnosis of the aneurysmal syndromes. On the other hand, in non-syndromic diseases the diagnosis is exclusively based on the presence of the aneurysm whose development can be age-dependent: extra-aortic traits are absent and therefore cannot contribute to the clinical suspicion of the disease.

3. Non-syndromic TAA

In children, non-syndromic TAA is uncommon and, when present, dissection is rare [18]. Non-syndromic Familial TAA (F-TAA) are caused by defects in the structural and functional proteins of vascular smooth muscle cells (vSMC), extracellular matrix (ECM), or Transforming Growth Factor (TGF- β) signaling pathway [12,19]. vSMC genes include *ACTA2* (smooth muscle alpha-actin), *MYH11* (myosin heavy chain 11), *MYLK* (myosin light chain kinase, which phosphorylates the regulatory light chain of myosin to initiate SMC contraction) and *PRKG1* (cyclic guanosine monophosphate-dependent protein kinase that controls SMC relaxation through phosphorylation of the myosin light chain). ECM genes include *Fibrillin 1* and *2*, *COL3A1*, *MFAP5* that encodes the extracellular matrix component MAGP-2 and *MAT2A* that encodes methionine adenosyltransferase II alpha (MAT IIa). TGF- β pathway includes *TGFBR1* (LDS type 1), *TGFBR2* (LDS type 2), *SMAD3* (LDS type 3), *TGF2* (LDS type 4) and *TGF3* (LDS type 5).

The most useful characteristics for suspecting non-syndromic genetic TAA include the young age of the patients, the absence of known factors that can, by themselves, cause the disease (atherosclerosis or hypertensive aortic disease), a family history of TAA/TAAD, and the presence of aortic valve abnormalities such as BAV. Genetic workup includes counseling, genetic visit, testing and family screening [1]. Genetic testing is now commonly performed by analyzing multi-gene panels and next generation sequencing (NGS) that is crucial for confirming the diagnosis [20]. Cascade genetic screening in families provides data for segregation studies. Interpretation of results generated by the analysis of multigene panels can be easy when mutations are known and proven to be pathological, while caution is required in cases of a novel, non-truncation predicting missense mutation.

TAA is usually asymptomatic unless its size is large enough to compress adjacent organ/structures causing symptoms that can be noticed by patients. In asymptomatic patients with negative family history, the diagnosis can be incidental (Fig. 1A) or coincide with the occurrence of aortic dissection in a patient who was previously unaware of the

disease (Fig. 1B and C). In these circumstances, clinical family screening including 2D-TTE of first-grade relatives should be regularly performed and may demonstrate the presence of other affected members in the family. As general rule, genetic testing does not substitute the clinical diagnosis [1] but it provides the specific diagnosis and the possibility of segregation studies only when the identified mutation is proven to be pathological and causally linked with the phenotype in the proband and family.

4. Syndromic TAA/TAAD

4.1. The most common syndromic TAA/TAAD: Marfan syndrome

The aortic aneurysm in MFS typically affects the root of the aorta (Fig. 2) and is characterized by slowly progressing dilation of the sinuses of Valsalva. In MFS, cardiovascular, skeletal, ocular, integumentary, nervous and respiratory systems are variably affected. Diagnostic criteria for MFS have been revised in 2010 [21]; aortic aneurysm, ectopia lentis (EL), proven positive family history and pathologic mutation are combined with a systemic score (≥ 7) derived from the sum of the values assigned to other traits (skeletal, non-EL ocular, nervous, integumentary, and lung) of the disease. Multimodality imaging (2D-TTE, CT and/or magnetic resonance) provides the complete assessment of the aorta and extra-aortic vessels [9,27]. Aortic diameters should be described as both absolute values and Z-scores, this latter being uniquely useful in children and adolescents [22]. About 90% of patients with MFS demonstrate phenotypic traits that are, by themselves, sufficient for the clinical diagnosis. A minority of patients shows isolated EL: after exclusion of isolated *FBN1*-related EL (ECTOL1), differential diagnoses include autosomal recessive diseases [ECTOL2 (*ADAMTSL4* gene); microspherophakia and/or megalocornea, with ectopia lentis and with or without secondary glaucoma (*LTBP2* gene)]. Less than 5% of patients who carry mutations in *FBN1* show (Fig. 1B and C) an aortic aneurysm as the unique or nearly unique trait (systemic score < 7). There is no cure for MFS but each trait of the syndrome can be managed. Medications that reduce hemodynamic stress include β -adrenergic blockers [23] and angiotensin II receptor blockers (ARBs) [15,23]. These drugs are indicated because defects in Fibrillin 1 cause excessive activation of TGF β and angiotensin II stimulates the expression of TGF β [15,24,25]. TGF β antagonists have been shown to attenuate or prevent disease manifestations in fibrillin-1-deficient mice including emphysema, skeletal muscle myopathy, myxomatous valve disease, and aortic aneurysm [24]. Numerous clinical trials have tested and are still testing the effects of ARBs with discrepant results [25]. Amongst all the clinical problems that may occur in MFS, aortic dissection is the most catastrophic. Preventive surgery should be considered when the aortic diameter approaches 50 mm. Smaller diameters may be considered an indication for surgery in the presence of risk factors such as family history of dissection, hypertension, and rate of change >5 mm/year [3].

4.2. A less common but more malignant TAA/TAAD: Loeys–Dietz syndrome

In the novel nosology of Loeys–Dietz syndromes the defining classifier is the disease gene. Although the original grouping of LDS1 and LDS2 was based on the phenotype (dysmorphic with prominent craniofacial traits for the type 1 and EDS-vascular-like for the type 2) [26], the identification of novel disease genes and the overlapping of emerging phenotypes, led to the classification of LDS syndromes 1–5 on the basis of the disease genes in the order of identification/description [27]. LD syndromes share TAA (Fig. 3), arterial tortuosity, and high-risk vascular phenotype. A variable combination of dysmorphic, craniofacial, skeletal and joint traits (from laxity to arthritis) is common in LDS patients. The same genes that cause LDS can also cause non-syndromic TAAs. This implies that the disease may be phenotypically silent and not apparent until its first manifestation that, in non-syndromic patients,

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