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HTAD patient pathway: Strategy for diagnostic work-up of patients and families with (suspected) heritable thoracic aortic diseases (HTAD). A statement from the HTAD working group of VASCERN

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ABSTRACT

Heritable thoracic aortic diseases (HTAD) are rare pathologies associated with thoracic aortic aneurysms and dissection, which can be syndromic or non-syndromic. They may result from genetic defects. Associated genes identified to date are classified into those encoding components of the (a) extracellular matrix (b) TGFβ pathway and (c) smooth muscle contractile mechanism. Timely diagnosis allows for prompt aortic surveillance and prophylactic surgery, hence improving life expectancy and reducing maternal complications as well as providing reassurance to family members when a diagnosis is ruled out. This document is an expert opinion reflecting strategies put forward by medical experts and patient representatives involved in the HTAD Rare Disease Working Group of VASCERN. It aims to provide a patient pathway that improves patient care by diminishing time to diagnosis, facilitating the establishment of a correct diagnosis using molecular genetics when possible, excluding the diagnosis in unaffected persons through appropriate family screening and avoiding overuse of resources. It is being recommended that patients are referred to an expert centre for further evaluation if they

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meet at least one of the following criteria: (1) thoracic aortic dissection (<70 years if hypertensive; all ages if non-hypertensive), (2) thoracic aortic aneurysm (all adults with Z score >3.5 or 2.5–3.5 if non-hypertensive or hypertensive and <60 years; all children with Z score >3), (3) family history of HTAD with/without a pathogenic variant in a gene linked to HTAD, (4) ectopia lentis without other obvious explanation and (5) a systemic score of >5 in adults and >3 in children. Aortic imaging primarily relies on transthoracic echocardiography with magnetic resonance imaging or computed tomography as needed. Genetic testing should be considered in those with a high suspicion of underlying genetic aortopathy. Though panels vary among centers, for patients with thoracic aortic aneurysm or dissection or systemic features these should include genes with a definitive or strong association to HTAD. Genetic cascade screening and serial aortic imaging should be considered for family screening and follow-up. In conclusion, the implementation of these strategies should help standardise the diagnostic work-up and follow-up of patients with suspected HTAD and the screening of their relatives.

1. Introduction

Heritable thoracic aortic diseases (HTAD) are rare pathologies with an incidence of approximately 1 in 5000 (Fletcher et al., 2020). They are characterised by great variability in presentation and natural history and are associated with a high risk of aortic dissection (Milewicz and Regalado, 1993). HTAD encompasses both syndromic and non-syndromic entities associated with thoracic aortic aneurysms or dissections that can in turn be sporadic or familial. These entities may be caused by genetic defects. Most of these conditions demonstrate an autosomal dominant inheritance pattern with incomplete penetrance, with the latter being mainly observed in non-syndromic HTAD. Therefore, in addition to the known genetic defects, interplay between environmental factors and several modifier genes is suspected. Although the number of genes involved in HTAD is steadily increasing, a significant number of patients/families with HTAD have no identifiable pathogenic variant, suggesting that other yet unknown disease genes and mechanisms exist. Genes identified to date can be broadly classified into three categories: (1) genes encoding components of the extracellular matrix (e.g. *FBN1, MFAP5, LOX and COL3A1*); (2) genes encoding components of the TGFβ pathway (e.g. *TGFBR1/2, TGFB2/3, SMAD2/3*); (3) genes encoding components of the smooth muscle cell contractile mechanism (e.g. *ACTA2, MYH11, MYLK, PRKG1*) (Faggion Vinholo et al., 2019; Milewicz and Regalado, 1993; Verstraeten et al., 2017).

In order to benefit from up-to-date professional care encompassing aortic growth monitoring and prophylactic surgery to prevent dissections/ruptures, a timely diagnosis is essential. This does not only increase life expectancy and quality of life, but also helps to avoid maternal complications and adverse outcomes during pregnancy and expedites access to specialists and adequate services and benefits. Furthermore, family screening, facilitated by genetic testing, could help identify other family members at risk and equally provide reassurance to patients when the diagnosis is ruled out.

Due to the increase in knowledge over the last years, with the recognition of many new entities, a need for a straightforward document describing the optimal "patient pathway" defined by professionals in the field throughout Europe was identified. At present, patient care is diverse across Europe, and national specialized centers and networks are not available everywhere. Hence, the aim of this document is to propose such a pathway to:

(1) improve patient care by reducing time to diagnosis
(2) facilitate the establishment of a correct diagnosis, using molecular genetics, when possible, which can help achieve more personalized treatment
(3) exclude the diagnosis in unaffected persons through family screening
(4) avoid overuse of financial and personnel resources.

This document focuses on the initial evaluation of patients with a suspicion of HTAD. It can be used both by non-specialized healthcare providers (HCPs) to guide them in choosing who to refer to a specialized center) as well as HCPs in specialized centers to aid in the standardisation of care across Europe.

Comparable patient pathways that can be applied to patients presenting with diverse clinical manifestations have to our knowledge not been published. Aortic disease oriented pathways can be found in guideline documents (Erbel et al., 2014; Isselbacher et al., 2022), which have a more focused approach compared to this document.

This document is an expert opinion reflecting strategies put forward by medical experts, and patient representatives, involved in the HTAD Rare Disease Working Group of VASCERN. **The HTAD Rare Disease Working Group** is one of the six Rare Disease working groups of the European Reference Network on Rare Multisystemic Cardiovascular Diseases (VASCERN), which covers a spectrum of syndromic and non-syndromic clinical entities with aortic manifestations. A total of 14 healthcare providers representing 8 EU countries, 2 additional cooperating centers from 2 countries and one patient advocate, representing the HTAD Patient Working Group, are members of the working group. The full list can be found on the website (www.vascern.eu). This pathway is a consensus at expert level. It was generated based on available guidelines when possible. Discussion items were listed and, where necessary, items were included in a questionnaire sent out for voting and discussion over monthly teleconference calls. This pathway describes what was considered an ideal pathway by the experts. However, adhering to this pathway may not be possible in all countries. Given the decreasing cost of genetic testing, it may become more easily available. We propose that this pathway is used as a guide when establishing local policies. It is available on the website of VASCERN (www.vascern.eu) and will be updated regularly. To the best of our knowledge, no other patient pathway has been published on this topic.

That being said, it is worth emphasising that defining "absolute thresholds" to decide whether or not to refer a patient for further evaluation is an impossible task and that many clinical scenarios cannot be captured in an algorithm or a pathway and will always require clinical expertise. Factors impeding the design of recommendations for referral of patients with a suspicion of HTAD include:

1. The age-dependent expression of many manifestations, rendering evaluation in children very challenging
2. The variability of the phenotype, and, in particular, the notion that syndromic manifestations are not necessarily required for a diagnosis of HTAD
3. The fact that, to date, clearly defined diagnostic criteria only exist for Marfan syndrome

Similarly, the expertise of people using these recommendations may vary with their background, so that the proposed scheme may have to be adapted to local expertise.

2. Pathway elements

(a) Thoracic aortic aneurysm (TAA)

Definition: TAA is defined as an aortic diameter at the level of the root, ascending aorta, arch or descending aorta up to the level of the

diaphragm that exceeds the normal value. In the general population, aortic diameters show a normal distribution. Hence, the probability of having a diameter above a given value can be derived from the z-score, which represents the number of standard deviations above the mean. Application of the z-score considers several factors that influence aortic diameter, namely patient age, sex, height, and weight. This is particularly relevant in childhood, but is also useful in adulthood to diagnose abnormal aortic diameters in subjects of various body sizes. Given that statistically only 2.3% of the general population is expected to have a z-score above 2 (and only 0.13% of the population a z-score above 3), a higher aortic z-score signifies a higher probability of an aortic abnormality that calls for further assessment. Different nomograms measuring the aorta from leading edge to leading edge (Campens et al., 2014; Devereux et al., 2012; Gautier et al., 2010; Roman et al., 1989; Rutten et al., 2021), or using an inner-to-inner diameter (Cantinotti et al., 2017; Lopez et al., 2010; Pettersen et al., 2008) have been proposed over the years. To avoid over- or underestimation of the z-score, the nomogram used for interpretation should match the method used for measurement. As a general rule, we propose the adoption of the most recently proposed method which covers children and adults and to use leading edge to leading edge aortic measurements (Campens et al., 2014). We also recommend z-scores using height in patients who are severely under- or overweight. (Devereux et al., 2012). However, the presence of multiple tools available underlines the imperfection of each of the calculations proposed, and comparison of various results may be helpful in difficult cases (online calculation https://www.marfan.fr/accueil/z-score-calculus). For follow-up purposes, it is recommended that, for a given patient, the same method and nomogram is applied consistently.

Measurement of aortic diameter to detect aortic aneurysm: TAAs are more frequent at the level of the aortic root or at the level of the tubular portion of the ascending aorta than in the aortic arch or descending thoracic aorta. Hence, views of both aortic root and ascending aortic diameters should be obtained during screening. The reference thoracic aortic measurement is usually acquired from a parasternal long-axis view using two-dimensional echocardiography. Leading edge to leading edge measurements in diastole are preferred (Goldstein et al., 2015; Lang et al., 2005). When a transverse view of the aortic root is obtained (usually during magnetic resonance imaging (MRI) or computerised tomography (CT)), the cusp-to-cusp measurement, which is the more comparable measurement to that obtained during echocardiography, should be used (Amsallem et al., 2015; Rodríguez-Palomares et al., 2016). Cusp-to-commissure measurements tend to systematically lead to lower values than echocardiographic measurements. For diagnosing aortic root aneurysm, transthoracic echocardiography (TTE) remains the preferred screening tool. However, the tubular aorta, arch and descending aorta may not always be easily visible on TTE, and MRI or CT might be required in these instances, with the choice of modality depending on local availability and patients' preference.

The variability of the aortic measurements depending on the technique used and the method of measurement is important to keep in mind when considering the calculation of the z-score and defining aortic dilatation, and also for evaluating progression of aortic root dilatation over time (Goldstein et al., 2015). When comparing serial studies to analyse for progression of aortic dilatation over time, side-by-side comparison of measurements using the same imaging modality and assessment method is recommended. Only differences in excess of 3 mm are to be considered significant.

Criteria for further investigation: The z-score threshold value above which to consider a TAA to warrant further investigation differs between adults and children.

For children, the proposed z-score threshold has been set at 3 in the latest diagnostic criteria for Marfan syndrome (MFS) published in 2010 (Loeys et al., 2010), because small differences have larger impact on z-score in children than in adults, and the observation that a moderate aortic dilatation observed in early childhood is often not present later in life (Gautier et al., 2010). However, whether this is still true with the more recent z-score nomograms remains unclear. We propose to use a similar z-score threshold of 3 to consider aortic dilatation to be significant in children (<18 y.o.). However, a z-score of >2 in a child with other systemic manifestations or progression of the z-score over time, should prompt referral to an expert centre. For those children with a z-score between 2 and 3 and no other clinical manifestations, we propose a repeated measurement after 1–2 years to evaluate progression or normalization.

In adults, confounding factors such as hypertension and aging are important, and can be independently responsible for aortic dilatation mainly at the level of the tubular aorta (Mori et al., 2019; Mulè et al., 2017). It is our recommendation to pursue diagnostic evaluation for HTAD in adults with an aortic z-score of 3.5 or higher irrespective of age or presence of hypertension, given that the latter alone is not a sufficient risk factor to explain such a degree of dilatation. When the z-score is between 2.5 and 3.5 (Campens et al., 2014), diagnostic evaluation is recommended at all ages if normotensive, and for subjects <60 years of age if hypertension is present.

Although the patient pathway outlined in this manuscript is focused on diagnosis, we want to point out that the criteria used to define thresholds for surgery commonly use unadjusted absolute aortic root diameters and not z-scores, which is related to the fact that studies about aortic dissection risk mainly report absolute diameters (Jondeau et al., 2012; Milleron et al., 2020). Z-scores do have significant advantages, especially in the pediatric population, but sources of limitations including measurement error, validity of nomograms, inconsistent use of BSA equations and uncertainty of the natural history of z-scores need to be taken into account (Curtis et al., 2016).

(b) Thoracic aortic dissection (TAD)

Definition: There are two types of TAD, type A and B, and both are rare entities. Type A has an incidence that ranges from 2.1 to 16.3/100,000 inhabitants (Wundram et al., 2020). Type B dissections may be slightly less frequent (Acosta and Gottsäter, 2019). The main risk factors for aortic dissection are older age, hypertension and underlying genetic aortopathy (Evangelista et al., 2018). For the purpose of this document, arterial hypertension is defined as blood pressure values exceeding 140/90 mmHg or patients treated with antihypertensive agents, in line with international guidelines (Williams et al., 2018). Hypertension leading to aortic dilatation/dissection is usually longstanding, or not well-controlled, and often unrecognised. TAD presenting in younger patients is more likely to have a genetic origin and is less likely to be linked to a history of hypertension or atherosclerosis (Januzzi et al., 2004). Intramural hematoma and pseudoaneurysms are usually seen in the setting of advanced atherosclerosis, with a lower risk of underlying genetic aortopathy, and should follow referral rules set for aneurysm/dissection only in the absence of atheroma.

Criteria for further investigation: We propose further evaluation of all patients with TAD if there is no history of hypertension and patients <70 years of age in the presence of hypertension.

(c) Bicuspid aortic valve (BAV)

Definition: BAV is a common entity, with an estimated prevalence of 1–2% in the general population (Braverman et al., 2005). In the absence of aortic stenosis or regurgitation, it can often go unnoticed. BAV is associated with a risk of earlier occurrence of aortic stenosis during late adulthood as well as TAAs, predominantly at the level of the ascending aorta, in approximately 50% of cases. The progression of these aneurysms remains unpredictable (Detaint et al., 2014; Verma and Siu, 2014). Some cases of BAV are familial with family screening efforts identifying BAV or TAA in approximately 10% of relatives (Cozijnsen et al., 2018; Galian-Gay et al., 2019; Massardier et al., 2020). Pathogenic variants in genes encoding for components of the TGFβ pathway have been associated with more frequent occurrence of BAV (Attias et al.,

2009). The concomitant presence of BAV in patients with an *FBN1* mutation has not been found to represent an additional aortic risk factor in patients with MFS (Milleron et al., 2019).

Criteria for further investigation: TAA in the presence of BAV should be worked up further as per guidance set out above. Patients with BAV but normal aortic calibre warrant further evaluation if they manifest additional systemic features or if they are familial.

(d) Medium-sized artery (MSA) aneurysms/dissection

Diseases of multiple medium-to-large arteries or recurrent events, even in the absence of TAA, should prompt referral to a specialized center for diagnostic evaluation. This is discussed in more detail in a dedicated pathway available at vascern.eu/expertise/rare-diseases-wgs/medium-size-arteries-wg.

(e) Extravascular features

Syndromic HTAD entities typically present with a combination of several extravascular features. Since some of these features may become apparent prior to the development of aortic disease, their recognition can be crucial to early referral to an expert centre for evaluation of possible HTAD.

Definitions:

Mitral valve prolapse is prevalent in patients with *FBN1* pathogenic variants (including MFS) and to a lesser extent in patients harbouring pathogenic variants in genes encoding for components of the TGFβ pathway (including Loeys-Dietz syndrome (LDS)) (Mühlstädt et al., 2019).

Ectopia lentis is most commonly associated with MFS (Adès et al., 2004; Sadiq and Vanderveen, 2013), but can also be a feature of other genetic disorders. A diagnosis of ectopia lentis should promptly trigger echocardiographic and genetic testing of the patient and familial ophthalmological screening. Equally, a suspicion of MFS or the presence of an *FBN1* pathogenic variant should prompt ophthalmological assessment for ectopia lentis.

Facial features such as dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia and high-arched palate are found in MFS (Table 1). Characteristic features of LDS include bifida uvula, cleft palate and hypertelorism.

Skeletal features are associated with some genes responsible for HTAD. Pectus excavatum (and, the less common albeit more specific, pectus carinatum, increased arm span, scoliosis (particularly with double curvature), arachnodactyly (positive wrist and thumb signs), flat feet, spondylolisthesis, kyphosis, reduced elbow extension and dural ectasia have been associated with MFS. Club feet and cervical spine instability can be present in LDS. However, several of these features are not specific to one condition. For example, scoliosis, pectus deformity, dural ectasia and flat feet can also be encountered in LDS, and many of these features can also be encountered in patients with genetic variants in other HTAD genes.

Table 1
Scoring of systemic features in Marfan syndrome (Loeys et al., 2010).

Systemic feature	Score
● Wrist sign	1
● Thumb sign	1
● Wrist AND thumb signs	3
● Pectus carinatum deformity	2
● Pectus excavatum or chest asymmetry	1
● Hindfoot deformity	2
● Pes planus	1
● Pneumothorax	2
● Dural ectasia	2
● Protrusio acetabuli	2
● Reduced upper segment/lower segment ratio AND increased arm span/height AND severe scoliosis	1
● Scoliosis OR thoracolumbar kyphosis	1
● Reduced elbow extension	1
● Facial features (at least 3 of 5): dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplastia, retrognathia	1
● Skin striae	1
● Myopia >3 diopters	1
● Mitral valve prolapse (all types)	1

Cutaneous features include striae, particularly of the shoulders (Ledoux et al., 2011) for MFS and easy bruising, dystrophic scarring, milia and translucent skin for LDS (Loeys et al., 2006).

Recurrent pneumothorax: The estimated frequency of recurrent pneumothorax in patients with MFS over the age of 12 years is 4–11% (Arnaud et al., 2021; Boone et al., 2019). Although infrequent, it is seen more commonly than in the general population where the estimated prevalence is 0.01% (Boone et al., 2019). The prevalence in LDS and other HTAD is currently unknown. However, pneumothorax in the absence of other features is rarely indicative of a diagnosis of HTAD and current guidelines do not recommend referral of patients for further evaluation of possible HTAD solely on the basis of a history of spontaneous pneumothorax (MacDuff et al., 2010; Schnell et al., 2018; Tschopp et al., 2015). Therefore, it is our recommendation that a diagnosis of MFS or related condition should only be looked for in patients with a history of spontaneous pneumothorax that also manifest other features suggestive of such genetic conditions.

Criteria for referral to a reference center: None of the above features alone are specific. It is the association of various features, not usually found in the general population, which carries a diagnostic value and should prompt further referral. In keeping with this thinking, a scoring system has been proposed in the latest Ghent nosology for diagnosing MFS (Loeys et al., 2010), and this is summarized in Table 1. As shown in this table, some features bear a higher weighting because they are more specific to the diagnosis of MFS and should thus prompt a higher suspicion. In the study by Mühlstädt and colleagues, the average MFS systemic score in adults was 6.6 ± 3.2 in MFS, 3.4 ± 3.8 in individuals with a *TGFBR1* mutation, 4.2 ± 3.7 in *TGFBR2* mutation carriers, and 2.1 ± 2.1 in those with a *SMAD3* variant (Mühlstädt et al., 2019). In children, the systemic score is generally lower and early diagnosis might be hampered by the absence of skeletal features at younger ages (Stheneur et al., 2014).

Based on these findings, we propose that a MFS systemic score of >5 in adults should trigger further investigation, while in children evaluation is indicated in the presence of a systemic score of >3. However, given that, as previously shown, patients carrying variants in one of the genes of the TGFβ pathway tend to have lower systemic scores than the ones being proposed above, we recommend that the combination of features specific for LDS like bifid uvula, craniosynostosis, hypertelorism or osteoarthritis should equally prompt referral. Some scores or specific features have been associated with TAA (Faggion Vinholo et al., 2019), such as the seven signs score for MFS (Sheikhzadeh et al., 2012; von Kodolitsch et al., 2015), and the so-called "thumb-palm-test" in non-syndromic HTAD (Blumel et al., 2021) and these may further help with screening. Equally, there are some features not listed in the Ghent nosology that have been separately associated with MFS (von Kodolitsch et al., 2015). Thus, the presence of intracerebral arterial aneurysms, simple renal cysts at an early age, congenital mydriasis, or congenital heart defects such as BAV, coarctation of the aorta and persistent ductus arteriosus should also raise suspicion.

(f) Family history

A positive family history is defined as the presence of at least one first or second-degree relative with a thoracic aortic aneurysm or dissection below the age of 70 years or sudden death below the age of 45 years in the absence of an alternative etiology. First-degree relatives of patient with HTAD or sudden cardiac death should undergo TTE (as well as other investigations in case of sudden death) and should be referred to an expert center in case of a finding of aortic dilatation on imaging. TTE

and referral of second-degree relatives can be considered on an individual basis if first degree relatives are not available for screening.

In summary, we are proposing that patients should be referred to an expert centre for further evaluation of possible HTAD in the following instances:

1) Thoracic aortic dissection
   a. at age <70 years with hypertension (age limit subject to modification)
   b. all ages in the absence of hypertension
2) Thoracic aortic aneurysm (aortic diameter at any level)
   a. Z-score >3.5 with or without hypertension
   b. Z-score 2.5–3.5 without hypertension (or <60 years old with hypertension).
   c. Z-score >3, a z-score >2 associated with other systemic features or progression of z-score in children.
   d. The same rules apply for TAA in the presence of BAV.
3) A first-degree family member with a HTAD with or without pathogenic variant in a gene known to cause HTAD
4) Ectopia lentis without other obvious explanation
5) A systemic score >5 in adults and >3 in children (Table 1)
6) A combination of features typical of LDS

The HTAD patient pathway is summarized in Fig. 1. In Fig. 2, we provide some illustrations of the most typical clinical manifestations of syndromic forms of HTAD.

3. Evaluation of the patient at the expert centre might include

(a) Cardiovascular imaging

TTE is the cornerstone diagnostic and screening imaging tool and is indicated in all cases of suspected HTAD in whom the presenting feature is not a TAA or TAD. Measurements should include the aortic root (sinuses of Valsalva) and ascending aorta (Goldstein et al., 2015; Lang et al., 2005). Mitral valve morphology and function, aortic valve and left ventricular function should also be evaluated and congenital heart defects should be looked for.

Complementary imaging of the vascular system by **MRI or CT** is indicated in documented or high suspicion of TAA, to.

(i) obtain baseline imaging which can be used for comparison if aneurysm growth is suspected during serial echocardiographic monitoring. This is proposed in all patients aged >18 years or upon transitioning to adulthood
(ii) exclude aneurysms at locations beyond the proximal aorta and to assess for arterial tortuosity (Ciurică et al., 2019).
(iii) optimize visualization of the proximal aorta (particularly the ascending aorta) when echocardiography is technically difficult (e.g. in the presence of pectus deformities)

MRI and CT scanning should be used according to local facilities. MRI is the preferred technique for follow-up in view of lack of cumulative radiation exposure, which is particularly relevant in younger patients, but CT scanning is often more precise. Both modalities should be used with ECG triggering to avoid motion artefacts and to facilitate reliable measurements of the aortic root and ascending aorta in a double oblique angulated fashion (Goldstein et al., 2015).

(b) Ophthalmological assessment

This is indicated in case of a suspicion of classical MFS and should include a slit lamp examination (Adès et al., 2004; Gehle et al., 2017).

(c) Skeletal and facial evaluation

The skeletal features reported in Table 1 should be assessed in all patients (features of MFS). Additionally, features of LDS should also be assessed, including hypertelorism, bifid uvula/cleft palate and (history of) club feet. Lastly, (history of) early onset and widespread osteoarthritis should be looked for.

(d) Family history

A three-generation pedigree should be established with particular attention for first and second-degree relatives with aortic dissection, aortic aneurysm, including its location, left ventricular outflow tract abnormality, and sudden death at young age (<45 years) by obtaining medical records to validate the diagnosis.

(e) Multidisciplinary discussion

The results obtained from the clinical evaluations should be

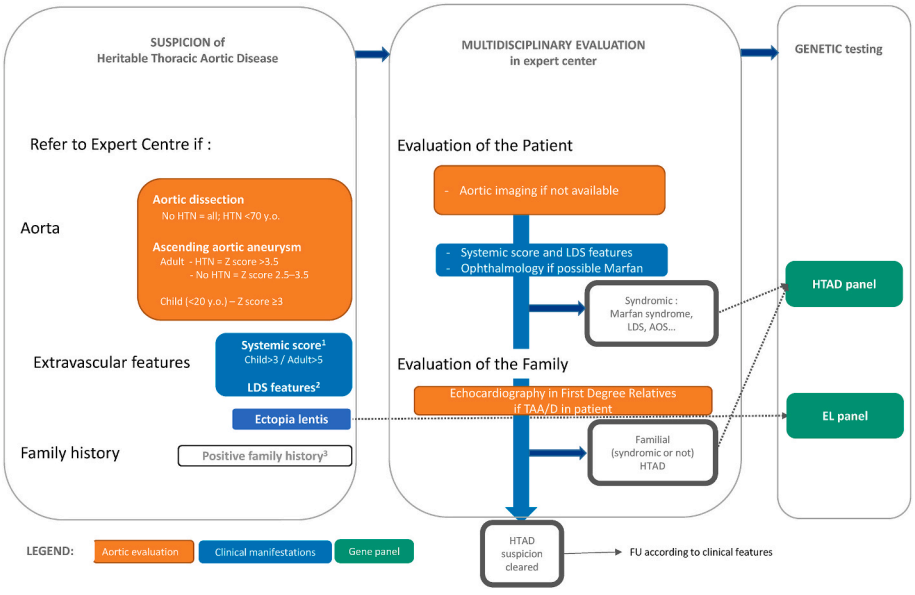

Fig. 1. Heritable Thoracic Aortic Disease (HTAD) patient pathway
Abbreviations: AOS = Aneurysm-osteoarthritis syndrome; EL = Ectopia Lentis; HTAD=Heritable Thoracic Aortic Diseases; HTN = arterial hypertension; LDS: Loeys Dietz Syndrome; TAA/D = Thoracic Aortic Aneurysm/Dissection; TTE = Transthoracic Echocardiography. Z score calculation in accordance with age, gender and technical method used by Campens, Devereux & Gautier (online calculation https://www.marfan.fr/accueil/z-score-calculus/).[1]Systemic score: see Table 1 (child with systemic score 3 or 4: consider re-evaluation after 3–5yrs until age 18yrs). [2]LDS features: bifid uvula, cleft palate, hypertelorism, clubfoot. [3]Minimum of 1 first or second-degree relative with: TAA/D (suspicion) < 70yr or sudden death <45yr.

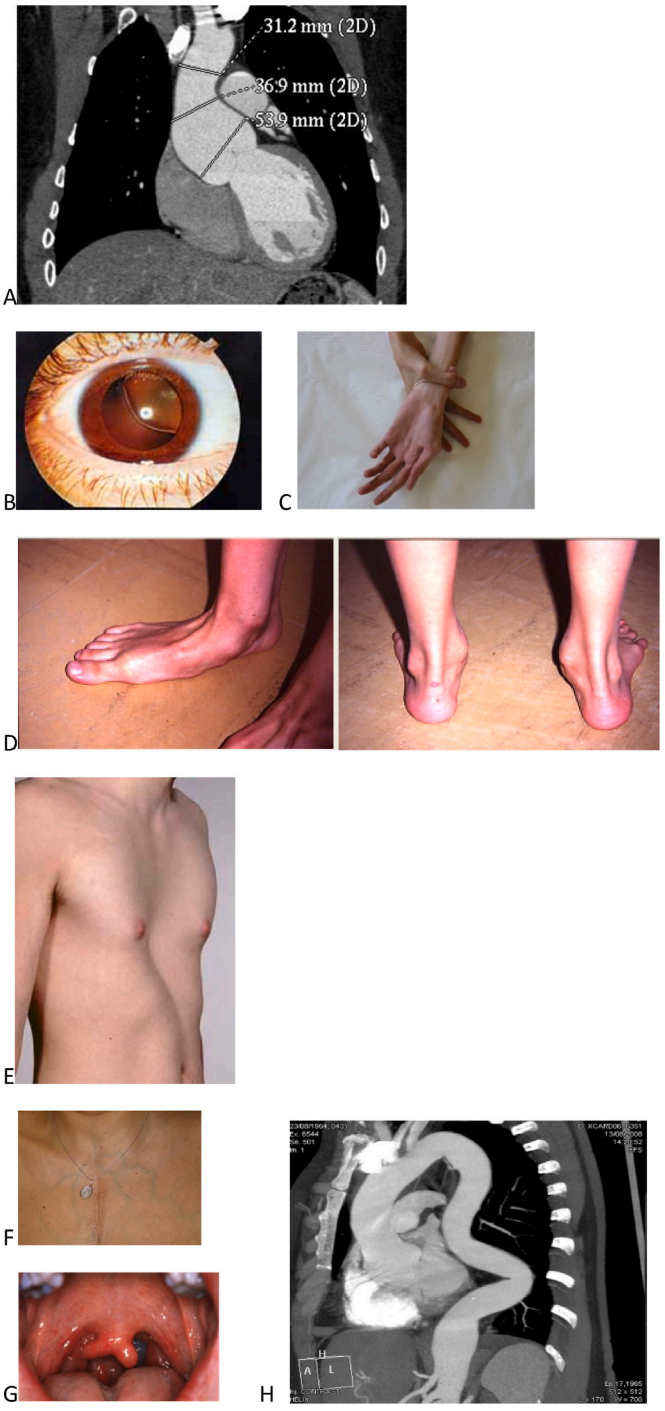

Fig. 2. Typical clinical manifestations in syndromic forms of Heritable Thoracic Aortic Disease:
A: Aortic root dilatation: common feature. B-E Features often observed in patients with a *FBN1* gene pathogenic variant (causal for Marfan syndrome): B: ectopia lentis C: wrist sign, D flat feet with hindfoot deformity, E pectus excavatum, F–H: Features often observed in patients with a pathogenic variant in genes encoding for TGFβ pathway components (causal for Loeys Dietz syndrome) F: skin translucency with visible veins & wide scar G: bifid uvula H: aortic tortuosity.

discussed in a multidisciplinary setting at the HTAD specialized centre, following which the indication for additional molecular genetic testing is evaluated. Different specialists such as orthopaedic surgeons, ophthalmologists, cardiologists, clinical geneticists and physiotherapists should be included in the diagnostic and management team at expert centers.

(e) Genetic testing

Genetic testing should be proposed when there is a high suspicion of an underlying genetic aortopathy and includes:

- patients with a familial form with or without hypertension (2 first or second-degree affected relatives) of thoracic aortic dissection or aneurysm (TAA/TAD) (Erhart et al., 2020; Wolford et al., 2019),
- sporadic TAA/TAD as defined above, at
  - any age, in the absence of arterial hypertension, or
  - <70 years of age in presence of hypertension
- patients with non-traumatic ectopia lentis compatible with MFS
- patients with a combination of TAAD and syndromic features of Marfan or LDS.

The decision to proceed with genetic testing should be initiated by physicians with experience in HTAD. That being said, the indications for genetic testing are largely dependent on local availability and are constantly changing as a consequence of technical progress making testing cheaper and hence more widely available.

Nowadays, multiple genes are tested within panels dedicated to specific diseases. The genes tested may vary from one center to another but should include the following:

- ectopia lentis: *FBN1* (Adès et al., 2004) (panel should also include *ADAMTSL4, LTBP2* (forms not related to HTAD)
- TAA or TAD or systemic features (Renard et al., 2018): genes with a definitive or strong association with HTAD: *ACTA2, COL3A1, FBN1, LOX, MYH11, MYLK, PRKG1, SMAD3, TGFB2, TGFBR1, TGFBR2.* This list is dynamic and will be updated regularly. The list of genes presently used in the various centers is available on the website of VASCERN.

The technical capacity to detect small intragenic copy number variants using NGS data is suboptimal, though algorithms have improved considerably over the last few years. Additional high-resolution copy number variant analysis should be considered in case of negative panels in patients with a high suspicion. Furthermore, after multidisciplinary discussion, in some specific cases, it may be necessary to consider whole exome or genome sequencing for diagnosis since deep intronic variants can be present, or other syndromes, like Alagille syndrome, Noonan syndrome and neurofibromatosis type 1, can have TAA as a rare manifestation. Despite this, a causative variant remains unidentified in many (roughly 80%) non-syndromic HTAD patients.

4. Family screening and follow-up

In cases where the pathogenic variant is known, it is proposed that family members undergo genetic cascade screening. Thereafter, only patients carrying the pathogenic variant will need serial aortic imaging. When the disease-causing pathogenic variant in the index patient is not known, follow-up by imaging (mainly TTE) of first-degree relatives depends on how many first or second-degree relatives have a dilated aorta.

- In familial TAAs (at least 2 affected relatives), aortic imaging should be performed yearly when the aorta is dilated and every 5 years when aorta is not dilated in first-degree relatives (Erbel et al., 2014). Previous reports suggest the age of 25yrs to start screening (Verhagen et al., 2018) – we recommend starting at the age of 18yrs. More frequent imaging may be necessary when the surgical threshold is approaching, when the aorta is dilating, or in case of more than mild aortic regurgitation.
- In sporadic TAAs (only one family member affected), only the affected patient requires follow-up, and a single screening

echocardiogram is deemed sufficient in adult relatives (Erbel et al., 2014) unless the first test is performed before the age of 40 years, in which case a further test after the age of 40 years could be considered (Verhagen et al., 2018). In case the measured aortic diameter is borderline, a second echocardiography after 5 years appears wise.

5. Conclusion

This referral pathway should help achieve standardisation of diagnostic workup and follow-up of patients with suspected HTAD and the screening of their relatives. It focuses on patients with both syndromic and non-syndromic forms of heritable thoracic aortic diseases. It is subject to updates over time with better recognition of new entities, and with the technical progress and increased availability of genetic testing.

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Data availability

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