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Practical clinical guidelines for the diagnosis and management of Marfan syndrome

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Section 1 General Introduction

1.1 Motivation for guideline development

Few original data on the birth prevalence of Marfan syndrome are available in the medical literature. The prevalence at birth was originally estimated at around 1/10,000 and the prevalence at 1/14,217 (Gray et al, 1994), but later estimates assume a prevalence of 2-3 per 10,000 (Judge & Dietz, 2005; Pyeritz, 2000), although the basis for these higher estimates is unclear. Based on the figures of Gray (1994) and a life expectancy with Marfan syndrome of 70 years (a figure based on little data), one arrives at an estimate of around 1,200 to 1,300 patients in the Netherlands, with 18 newborns per year.

Marfan syndrome is an autosomal dominant, multisystem disorder in which the heart and aorta, skeleton and eyes are the major affected organs. Due to the variety of disease expression, the wide variability and the hereditary nature of the condition, there is often a range of specialists involved in the care of a patient with Marfan syndrome.

Because the disease is relatively rare, 4 expert centres (Marfan clinics) have been established in the Netherlands. These centers provide Marfan syndrome diagnostics when a diagnosis is suspected on clinical grounds and ensure adequate clinical assessment and treatment. While the Marfan clinics are in close contact with one another, there are nevertheless differences in the approach to and organisation of care.

Moreover, there is currently no uniform policy for referral from primary and secondary centres to a Marfan clinic. In order to develop a uniform policy regarding the referral, diagnosis and treatment of Marfan patients, the scientific societies involved in the care for Marfan patients have decided, following an initiative of the Dutch Society of Clinical Genetics (VKGN), to develop a guideline with uniform, and as far as possible, evidence-based recommendations.

The development of the guideline was funded by the Stichting Kwaliteitsgelden Medisch Specialisten (SKMS). The Department of Professional Quality Support of the Dutch Order of Medical Specialists provided methodological support.

1.2 Aim of the guideline

The guideline provides recommendations for physicians regarding referral policy, which amongst others provides guidelines regarding the characteristics required to indicate a referral to a Marfan clinic. In addition, recommendations are made for care providers at Marfan clinics regarding the diagnostic procedure, the logistics thereof, the clinical assessment and treatment of Marfan patients and family studies. Specific recommendations regarding prenatal diagnosis, pregnancy and childbirth are also made.

No recommendations are provided for the treatment of disorders or problems that occur more frequently in Marfan syndrome than in the normal population, but which do not require treatment other than that appropriate in non-Marfan patients.
Patients with Marfan syndrome, organised in the Contactgroup Marfan Netherlands, were involved in the creation of this guideline and made recommendations for the organisation of care.
With this guideline, the working group hopes to create a tool for the provision of uniform care in Marfan syndrome.

1.3 Delineation of the guideline

Description of the problem and clinical questions.
The working group has formulated a number of clinical questions (see Appendix 1) that form the basis for the various sections of this guideline. The guideline does not aim to describe the entire process of clinical care, but focuses on specific bottlenecks.
The guideline covers the diagnosis and treatment of patients with Marfan syndrome and is based on new criteria established in 2010, "the revised Ghent nosology for the Marfan syndrome" (Loeys et al, 2010), subsequently referred to as the Ghent II criteria. The guideline refers to the original Ghent criteria as Ghent I (De Paepe et al, 1996).

1.4 The intended users of the guideline

The guideline is primarily aimed at all healthcare professionals involved in the detection, diagnosis, monitoring and treatment of patients with Marfan syndrome: GPs, (paediatric) cardiologists, paediatricians, thoracic surgeons, clinical geneticists, ophthalmologists, gynaecologists, orthopaedic surgeons, midwives, paediatricians and doctors at health clinics. The directive is therefore not only intended for specialists linked to a Marfan clinic. The secondary target group is that of patients with Marfan syndrome.

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Section 2 Methodology of Guideline Development

2.1 AGREE

This guideline has been prepared on the basis of the "Appraisal of Guidelines for Research & Evaluation II" (AGREE II) instrument (www.agreecollaboration.org). This is a widely accepted international instrument for the assessment of the quality of guidelines.

2.2 Working group

For the development of the guideline, a multidisciplinary working group was established in 2010, consisting of representatives from all relevant specialties involved in the assessment and care of Marfan syndrome. The working group consisted of clinical geneticists, cardiologists, a cardiothoracic surgeon, ophthalmologists, a gynaecologist, a paediatrician/-cardiologist, orthopaedic surgeons, a molecular geneticist and an anaesthetist (see Members of the Working Group).

The working group members were mandated to participate by their professional associations. The group worked for two years on the creation of the guideline.

2.3 Declarations of conflicts of interest

Members of the working group have declared in writing whether they have maintained, over the last five years, a (financially supportive) relationship with commercial enterprises, organisations or institutions related to the subject of the guideline.

2.4 Patient participation

During the development of the guideline, a specific focus was to appraise the perspective of the patient. The working group included a representative of the patient organisation Contact Group Marfan Netherlands. In addition, a patient focus group was organised. The discussions within the focus group were summarised in a report that was made available to members for verification and possible additional comments. A summary of this report (Appendix 3) was used by the working group in the preparation of the guideline, and finally, members of the focus group were asked to comment on the draft guideline.

2.5 Analysis of critical issues

Particularly difficult issues were identified during the preparatory phase, in cooperation with the chair of the working group. These issues were discussed in the working group, and on this basis clinical questions were formulated.

2.6 Clinical questions and outcome measures

Clinical questions were formulated by the working group based on critical issues. When possible, the most important and patient-relevant outcome measures were identified for each clinical question.

2.7 Literature search strategy

The basis for the guideline is provided by evidence from published scientific research. During the exploratory search, the Cochrane Library was searched and existing guidelines were specifically sought in (inter)national guideline clearinghouses that allow online searches.

Because not all clinical questions lend themselves to a systematic literature search, prior agreement was made to limit systematic literature searches to questions regarding treatment and to those related to pregnancy and childbirth.

Based on specific search terms, the electronic databases Medline and Embase were searched for published scientific studies relevant to the clinical questions formulated. If necessary, searching for additional studies was carried out. Initial searching focused on (systematic reviews or meta-analyses of) randomised controlled trials (RCTs). In the absence of RCTs, searching was resumed; now focusing on prospective comparative controlled trials and prospective non-comparative studies. Languages were limited to English, Dutch and German.

The working group members selected items by relevance. In addition, studies were extracted from reference lists of retrieved literature. For certain clinical questions, this resulted in additional relevant articles. The selected articles were used to answer the clinical question.

For the remaining clinical questions, the available scientific evidence proved to be insufficient. To answer these questions, the expertise of the working group members was elicited, supported by scientific literature when available. Because Marfan syndrome is a rare disorder, the available literature is often limited to case series and small patient groups.

2.8 Strategy for assessing literature

Literature reviews were carried using the EBRO methodology. Individual studies were assessed for study approach/design. Following this assessment, the level of study evidence was determined according to the classification described in Table 2.1 and Table 2.2. A summary of the literature and the level of evidence of the relevant studies can be found in the guideline text under the headings, ‘summary of the literature’ and ‘conclusion’.

Table 2.1. EBRO classification of individual study quality

Evidence level	Diagnostic accuracy of research	Injury or side effects, etiology, prognosis
A1	Meta-analysis of at least 2 independently conducted studies of A2-level	
A2	Research conducted in relation to a reference test (gold standard) with predefined cut-off values and independent assessment of results, with a sufficiently large series of consecutive patients, all of whom have undergone both the index and reference tests	Prospective cohort study of sufficient size and follow-up, which adequately controlled for confounding and with sufficient exclusion of selective follow-up
B	Research relative to a reference test, but not with all the features listed under A2	Prospective cohort study, but not with all the features listed under A2 or a retrospective cohort or case-control study
C	Non-comparative study	

Table 2.2. Level of evidence supporting a conclusion

Conclusion based on	
1	Study of level A1 or at least two independently conducted studies of level A2
2	One study of level A2 or at least two independently conducted studies of level B
3	One study of level B or C
4	Expert opinion

2.9 Considerations

Before making a specific recommendation, in addition to the scientific evidence, other factors must be considered including the expertise of the working group members, patient preferences, costs, availability of facilities or organisational aspects. These factors are, in sofar as they have not been scientifically investigated, listed under the heading 'considerations'.

2.10 Recommendations

The recommendations provide an answer to the central clinical question and are based on both the available scientific evidence and on the most important considerations.

2.11 Comment and authorisation phase

The draft guideline was presented to the relevant (scientific) associations for comments. The comments were gathered and discussed within the working group. In response to the comments, the draft guideline was adapted and finalised by the working group. The final guideline was then sent to the directors of the (scientific) associations for authorisation.

2.12 Implementation

During the development of the guideline, the implementation and feasibility of the recommendations were already taken into account. Consideration was given to factors that could either promote or hinder the introduction of the guideline in practice. The guideline has been distributed to all relevant professional groups and institutions, and an electronic version of the guideline will be published. The electronic version will be available for download from the VKGN website and from other participating organisations, and from the Kwaliteitskoepel: www.kwaliteitskoepel.nl. A summary of the guideline will be submitted to the Netherlands Journal of Medicine and to other relevant journals. In order to bring the guideline to the attention of the target audience, a symposium will also be organised.

2.13 Legal implications of the guideline

Guidelines are not laws, but are based on evidence-based insights and recommendations that caregivers must satisfy in order to provide high-quality care. Since these recommendations are mainly based on 'general evidence for optimal care of the average patient', the professional autonomy of healthcare providers allows them deviate from the guidelines in individual cases, where necessary. Even deviation from the guidelines may be necessary in certain situations. In cases where the guideline is not followed, any deviation should be justified and documented and, where relevant, this should be following consultation with the patient.

2.14 Revision

The board of the VKGN will decide whether the guideline is still current, not later than 2017. If necessary, a new working group will be formed to revise the guideline. The validity of the guideline will be earlier curtailed if new developments necessitate the initiation of a revision process.

The Dutch Society of Clinical Genetics (VKGN) is the originator of this guideline and is as such primarily responsible for the topicality of the guideline. Other scientific associations participating in the guideline or users of the guideline share responsibility, and should inform the VKGN on relevant developments within their field.

Section 3 Diagnostics

Introduction

Marfan syndrome is a multisystem disorder with a highly variable expression, leading to difficulties in detection and diagnosis. A diagnosis of Marfan syndrome is made on the basis of clinical and genetic findings, whereby use is made of the Ghent II criteria (Loeys et al, 2010). These criteria are a revision of the Ghent I criteria (Chapter 3 of this thesis, De Paepe et al, 1996). Based on these criteria and related critical comments, recommendations are made which form the basis for a diagnosis of Marfan syndrome.
From the question of the selection of an appropriate diagnostic procedure, the question arises as to the minimum characteristics indicating diagnostics. Again, recommendations are made, including the most appropriate diagnostic procedure.

Summary of the literature

What are the diagnostic criteria for Marfan syndrome?
The possible characteristics of Marfan syndrome are listed in Appendix 2. This table shows the characteristics used in the Ghent I (De Paepe et al, 1996) and Ghent II criteria (Loeys et al, 2010). The list is not comprehensive, and although not all features are included in the Ghent criteria, they may nevertheless contribute to the recognition of Marfan syndrome.
Sponseller et al. (2010) have compared the frequency of occurrence of a number of Ghent criteria (mainly facial and skeletal abnormalities) in genetically confirmed Marfan patients (n = 183) and in a control group (n = 1257) and based on this, determined the sensitivity and specificity of the different characteristics (Sponseller et al, 2010).

1. *Facial features*
   All facial features are subjective and are almost never objectified in size or number. Despite this, facial features show a high sensitivity. A high palate with irregular dentition is no longer included as a diagnostic criterion in Ghent II, due to a low specificity.
2. *Skeletal features*
   Skeletal features can be partly objectively determined using measurements and radiographic examination. This is the case for arachnodactyly, in which use is made of the wrist and thumb sign. The thumb sign is positive if the distal phalanx of the thumb protrudes beyond the ulnar border of the hand at maximum adduction. The wrist sign is considered positive if the top of the thumb overlaps the entire nail of the little finger when circling the wrist.

Bodily proportions can be measured, with a span/length ratio of 1.05 or more being considered abnormal in the absence of scoliosis. When determining relatively long legs using the Ghent II criteria, normal values for the upper and lower ratios are given but these lack literature references. For acetabular protrusion and scoliose, standardised measurements are applied to a radiograph of either the pelvis or the spine (Sponseller et al, 2006).

3. *Cardiovascular features*

   In the most recent criteria, the greatest weight is given to a dilatation of the aortic root or aortic dissection type A. The combination of a dilated aortic root and a dilatation of the pulmonary artery is a strong indicator of Marfan syndrome (Nollen et al, 2002). Mitral valve prolapse is included in the systematic score. In a study of 52 relatively young patients with Marfan syndrome, aged between 3 and 28 years, 43 patients (83%) showed an aortic root dilatation and 46 (88%) showed a mitral valve prolapse (van Karnebeek et al, 2001).

   For the implementation and interpretation of cardiovascular imaging, see section 4.

4. *Ocular features*

   Until recently, diagnosis based on the Ghent I criteria included scoring for both major and minor criteria in which various ophthalmologic abnormalities were attributed a diagnostic value. The number of ophthalmologic abnormalities that contribute to the diagnosis of Marfan syndrome is greatly reduced in the Ghent II criteria, and only lens (sub)luxation and myopia of more than three diopters are still included. Lens (sub) luxation is the only major ophthalmologic criterion in both the Ghent I and Ghent II criteria.

   A literature review by Nemet et al. (2006) describes the main ocular features of Marfan syndrome. Maumenee (1981) described eye diseases in a population of 160 Marfan patients from 0-60 years of age. Lens (sub)luxation or *ectopia lentis* is a known feature of Marfan syndrome, with a reported incidence varying from 50 to 87% (Nemet et al, 2006). The luxation is usually (but not always) bilateral and towards temporal-top (Maumenee, 1981; Nemet et al, 2006). In rare cases (2-3%) full *luxatio lentis* may occur, resulting in a lens free in the vitreous humourand (non-iatrogenic) aphakia (Nemet et al, 2006). A literature review by Dureau (2008) described the pathophysiology of lens (sub) luxation and attributed it to poor quality zonular fibres. In the case of Marfan syndrome, these fibres are stretched or even broken, permitting the lens to luxate (Dureau, 2008). Myopia greater than 3D is poorly indicative and is thus considered a less important criterion in the systematic score for the Ghent II criteria. Myopia is believed to occur in 34-44% of Marfan patients, compared with 4.8% of the normal population (Nemet et al, 2006). In a study of the level of myopia in Marfan syndrome patients, 50% of patients

showed myopia of 3D or more (Nemet et al, 2006).

Other ophthalmic characteristics that often affect the eyes of Marfan patients include iris hypoplasia, iris transillumination and iridodonesis. A flat cornea has also been described in the eyes of patients with Marfan syndrome. Heur (2008) compared the results of keratometry and central cornea thickness (CCT) from 62 Marfan patients (mean age 22.3 years) with those of 98 controls (mean age 19.3 yrs). The Marfan patients had a significantly lower outcome on keratometry and CCT than the controls. Peripheral retinal degeneration and retinal detachments occur in between 5 to 25.6% of patients with Marfan syndrome. These complications are more common in eyes with lens(sub) luxation and/or a long axis length (Nemet et al, 2006).

5. *Pulmonary*

   Spontaneous pneumothorax contributes to the systematic score. In a retrospective study of 166 patients aged 13 or older, 4.8% had experienced pneumothorax one or more times. Two of the 8 patients had experienced a pneumothorax twice or even several times (Karpman et al, 2011).

6. *Skin*

   Conspicuous striae at unusual locations count towards the systematic score, under the condition that the striae are not the result of significant weight change or pregnancy. Locations defined as unusual under the Ghent II criteria include the middle of the back, the lumbar region, upper arm, axilla region and hips (Loeys et al, 2010).

7. *Dura*

   Under the latest criteria, lumbosacral dural ectasia are now included in the systematic score. The method commonly used in the Netherlands to determine dural ectasia is that of Oosterhof (Oosterhof et al, 2001); this method has a high sensitivity and specificity, of 95% and 98%, respectively. The gold standard used was the presence (n = 44) or absence (n = 44) of Marfan syndrome based on clinical and genetic criteria. However, when comparing the method of Oosterhof with two other methods, a strikingly high level of dural ectasia was found in the control group. Using the Oosterhof method, Weigang found a sensitivity of 94% and a specificity of 57% (Weigang et al, 2006). In an observational study of 33 patients with features of Marfan or Loeys-Dietz but without genetic abnormalities, Sheikzadeh reported high levels of dural ectasia in individuals with non-specific connective tissue abnormalities but without Marfan syndrome (Sheikhzadeh et al, 2010).

8. *Other organ systems*

   Recurrent inguinal or umbilical hernia, incisional hernia, and reduced fat and muscle are not specific to Marfan syndrome but are very common. These features are no longer part of the diagnostic criteria.

9. *Family*

   Having a first-degree relative with Marfan syndrome carries significant weight in the Ghent II criteria.

10. *DNA*

    Marfan syndrome is usually caused by mutations in the *FBN1* gene, which codes for the protein, fibrillin-1. In a recent publication by Sheikzadeh, a mutation in *FBN1* was detected in 80% of the patients who met the original, the new or both Ghent criteria (Sheikhzadeh et al, 2011). The Ghent II criteria attributes considerable weight to causal mutations in the *FBN1* gene.

Neonatal Marfan syndrome

The debate in literature as to whether neonatal Marfan syndrome should be seen as a separate entity, or as a very severe form of Marfan syndrome, remains unresolved. Hennekam provided arguments supporting the limitation of the term 'neonatal Marfan syndrome' to newborns with severe mitral and/or tricuspid valve insufficiency and infantile emphysema (Hennekam, 2005). These children almost always die before the 2nd year of life due to progressive valve dysfunction and heart failure. Similarly to children with neonatal Marfan syndrome, children with a severe expression of Marfan syndrome may display serious skeletal abnormalities, lens (sub)luxation, aortic root dilatation and elastic skin, but almost never show life-threatening valve dysfunction. Neonatal Marfan syndrome (as defined by Hennekam) is almost always de novo (Stheneur et al, 2011).

What is the policy in the case of a newborn with 50% risk of Marfan syndrome?

This question leads to the question of what is the earliest age at which Marfan syndrome can present with features that may require treatment. The literature indicates that it is extremely rare for a child with classic Marfan syndrome to undergo cardiovascular surgery in the first year of life. Everitt et al. (2009) conducted a retrospective study in children with Marfan syndrome, and of the 196 patients, 18 (9%) had surgery in childhood. The youngest age at the time of the first cardiovascular surgery was 8 years. This is in contrast to the age of 1 in cases of neonatal Marfan syndrome and Loeys-Dietz syndrome (Everitt et al., 2009).

Conclusions

Level 4	The clinical diagnostic criteria for Marfan syndrome include abnormalities of the face, the skeleton, the cardiovascular system, the eyes, lungs, skin and the dura. In addition, DNA abnormalities (pathogenic mutations) and family history are also important. Aortic root dilatation, lens (sub)luxation, a first-degree relative with Marfan syndrome and a pathogenic mutation are the main criteria on which the diagnosis is based. D Loeys et al., 2010

Considerations

In this guideline the diagnostics of Marfan syndrome are based on the Ghent II criteria. In addition, the following considerations are taken into account:

1. General

   In order to avoid unnecessary diagnostics in cases of individuals with non-specific features of Marfan syndrome, an initial examination by a clinical geneticist affiliated to a Marfan clinic should be considered. The geneticist can assess whether additional diagnosis is necessary. Specific characteristics, such as aortic root dilatation/dissection without an obvious cause or a lens (sub)luxation, warrant extensive investigation.

2. Physical examination

   The physical examination is preferably carried out by a specialist with experience in Marfan syndrome. Most of the external characteristics of Marfan syndrome are non-specific and can only be subjectively determined. Appendix 2 describes the physical characteristics of Marfan syndrome.

   The Ghent II criteria assume a specific upper/lower segment ratio when determining relative leg length, but this is challenging to measure. The preference of the working group is for the measurement of the sitting height/length ratio, as robust normal values are available (Talma, 2010).

   The working group notes that striae are common in the middle of the back, the hips and lumbar region in the general population, and therefore expresses reservations regarding the inclusion of this criterion in the Ghent II criteria. The working group therefore recommends the inclusion of striae as a systematic criterion only when

present in places other than the abovementioned locations and when not associated with weight change. Marfan syndrome is characterised by striae particularly on the shoulders, upper arms and around the axilla.

3. Ophthalmological examination

Only two ophthalmological features score points on the diagnosis under the Ghent II criteria, lens (sub)luxation and myopia of more than three diopters.

Assessing lens position should occur at maximum mydriasis, using slit lamp examination. This is the only way in which lens (sub)luxation can be determined with certainty, as the condition can manifest itself in a very subtle manner. In some cases, only an irregular lens edge (notching) due to a single stretched zonula fibre is noted.

A refraction test should take place in all patients. The strength of existing spectacles or contact lenses is often the starting point in such cases. In young children, where subjective visual acuity and refraction measurement is not possible, the objective refraction should be determined using cycloplegic retinoscopy.

In order to calculate the degree of myopia, the value determined for the spherical equivalent of the cylinder is added to the value of the spherical refraction.

4. DNA research

The pathogenic effect of mutations, and thus the causal relation to Marfan syndrome, is insufficiently treated in the Ghent II criteria.

If the presence of an *FBN1* mutation is important for the diagnosis, this can only be taken into account if, in the opinion of an appropriately qualified clinical molecular geneticist, the mutation is pathogenic. When in doubt as to the pathogenicity of the mutation, it should not be included in the diagnostic criteria. When a mutation is not clearly pathogenic, additional research can be considered such as analysis of mRNA or protein from cultured fibroblasts, or DNA analysis of the mutation in the family.

If no clearly pathogenic mutation in *FBN1* is found, this should give rise to serious doubts regarding the diagnosis of Marfan syndrome and invoke a differential diagnostic consideration of whether there are grounds to investigate other genes.

5. X-ray diagnosis

X-ray diagnosis for acetabular protrusion and scoliosis is rarely necessary in the context of diagnosis, but can be indicated in the case of complaints or as an adjunct to therapy.

6. Diagnosis in children

The exclusion of a diagnosis of Marfan syndrome in children on clinical grounds alone is either not possible or difficult, especially in young children, as symptoms may arise later in life.

a. Child with a parent with both Marfan syndrome and a mutation in *FBN1*. DNA testing can determine whether the children of a parent carrying a pathogenic mutation in the *FBN1* gene will themselves develop Marfan syndrome. DNA testing can be offered in the first year of life so that, following confirmation of a mutation, an initial paediatric cardiological examination can be carried out to exclude rare aortic or valve problems that already require care in the first year of life. If possible, the first physical and ophthalmic examinations can also be conducted by a Marfan clinic. An initial ophthalmological examination in the first year of life is indicated for the early detection of cases at risk for serious lens luxation with a danger of amblyopia. The child will be monitored more or less frequently, depending on the findings.

b. Child with a parent with Marfan syndrome, but without a known *FBN1* mutation. In children with a 50% chance of developing Marfan syndrome but with an affected parent in whom no *FBN1* gene mutation was found, it is recommended that the initial study take place in the first year of life (physical, paediatric cardiological and ophthalmological examinations). If no indications are found, it is recommended that the child be re-examined at around the ages of 5, 12, and 17 years (Canadas et al, 2010). If there is still no evidence of Marfan syndrome, then after multidisciplinary consultation, the child can be discharged from follow-up and depending on the presentation in the family, a cardiologist at a peripheral centre can monitor the individual every five years. If evidence of Marfan syndrome is noted by the first birthday, more frequent monitoring can be agreed, depending on the findings.

c. Child with a negative family history.

In non-familial cases of children suspect for Marfan syndrome, without a DNA abnormality and with adequate clinical suspicion, it is recommended that the clinical examination be repeated at the ages of 5, 12 and 17 years. Given the high sensitivity of DNA analysis in the diagnosis of Marfan syndrome, only a very small number of children will fall into this group. If an *FBN1* mutation is found, the child will be treated as a confirmed Marfan syndrome case even if the clinical criteria are not yet met. This situation is referred to as 'potential Marfan syndrome' in Ghent II, a rather confusing term.

Recommendations

I. *Refer all patients with the following features for assesment by a specialist in Marfan syndrome, preferably in association with a Marfan clinic:*
- Aortic root dilatation or dissection of the thoracic aorta without obvious cause, or
- (Sub)luxation of the lens, or
- First-degree relative with Marfan syndrome.

II. *Refer* patients with less specific features of Marfan syndrome to an experienced specialist in Marfan syndrome, assessing the appropriate diagnostic route based on the features.

III. *Criteria used to diagnose Marfan syndrome:*
The Ghent II criteria are applied but with the following reservations:
- Striae in the middle of the back, the hips and lumbar region are not counted as systematic criteria. Striae on the shoulders, upper arms and around the axilla are counted if not associated with weight change.
- In the adult population, absolute values are used for diagnosis of aortic root dilatation. See section 4.

IV. *Standard diagnostic examination in cases of suspected Marfan syndrome:*
The following tests are advised in cases with an adequate suspicion of syndrome:
- Complete physical examination and family history;
- Cardiological examination including ultrasound of the heart and thoracic aorta;
- Eye examinations, including slit lamp examination in full mydriasis and measurement of the refractive error;
- DNA-analysis.

V. *Diagnosis in children*
- Perform DNA-analysis in the first year of life, in a child with a 50% chance of Marfan syndrome and a known FBN1 mutation in the father or mother, to exclude or confirm the diagnosis Marfan syndrome.
- If the diagnosis cannot be established or excluded with certainty in a child with a 50% chance of Marfan syndrome, re-examine the child around the ages of 5, 12, and 17 years.
- A neonate with pronounced physical characteristics of Marfan syndrome should be examined by a paediatric cardiologist, for suspected neonatal Marfan syndrome, at the first suitable moment.

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Section 4 Diagnostic Imaging of Aortic Root Dilatation

Introduction

The presence and extent of aortic root dilatation plays a central role in the diagnosis, monitoring and treatment of patients with Marfan syndrome. Various non-invasive techniques can be used for imaging of the aorta, with echocardiography as the standard approach, and MRI and CT providing additional information where necessary. Since absolute cut-off values are used in adults, both for the diagnosis of aortic root dilatation and as an indicator for preventive aortic root replacement, standardised methods of measurement and uniform normal values of great importance.

Summary of the literature

Echocardiography

International guidelines for the performance of echocardiography are available for both adults and children (Lang et al., 2005; Lopez et al., 2010).

The proximal portion of the ascending aorta is imaged in a parasternal long-axis view. Diameters are measured at the level of the aortic annulus, aortic root (largest diameter at the level of the sinus of Valsalva), sinotubular (ST)-junction and the ascending aorta half a centimetre above the ST-junction. Confusion arises because, according to the guidelines of the American Society of Echocardiography (Lang et al., 2005), these measurements should be taken at end diastole in adults, while the paediatric guideline (Lopez et al., 2010) of the same American Society advises the measurement of the dimensions during mid-systole.

Discussion is still ongoing as to whether the front wall of the aorta should or should not be included. This will be concurrently measured during the *leading edge to leading edge* measurement, but not by the *inner edge to inner edge* measurement technique. Commonly used normal curves, such as those of Roman (Roman et al., 1989), are based on leading edge to leading edge measurements and this seems to be the main reason why this measurement is recommended in the existing echocardiography guidelines for adults (Lang et al., 2005).

In contrast, the paediatric guidelines recommend the inner edge to inner edge measurement technique (Lopez et al., 2010).

The international guidelines (Lang et al., 2005, Lopez et al., 2010) favour two-dimensional aortic measurements rather than M-mode measurements because the aortic root moves

relative to the cursor line during the cardiac cycle, resulting in a systematic underestimation (of 2 mm) of the maximum diameter of the aortic root at the level of the sinus of Valsalva (Roman et al., 1989). It is worth noting that this observation was not confirmed in a study by Rozendaal et al. (1998).

The normal aortic root dimensions in adults differ between males and females, and are also influenced by posture and age. Nevertheless, absolute cut-off values are generally used for the diagnosis of aortic root dilatation or as indications for aortic root replacement. Biaggi et al. (2009) analysed ultrasound data (leading edge to leading edge in end systole) for 1,799 patients without cardiac disease and found that a size of ≥46 mm in men and ≥43 mm in women was abnormal. According to the curves developed by Biaggi, the maximum P95 diameter is 42 mm for men (age 70 years, BSA 2.1) and 38 mm for women (age 70 years, BSA 1.9).

Depending on age and BSA, smaller diameters can already be considered abnormal. Pelliccia et al. (2010) examined 2,317 athletes and found that a diameter of >40 mm in men and >34 mm in women fell outside the normal range (leading edge to leading edge in end diastole). Radonic et al. (2011) studied 38 healthy subjects with a large BSA and found a maximal aortic root diameter of 38 mm (echo, leading edge to leading edge in end diastole). Based on these findings and the literature, these authors suggested that an aortic root of >40 mm is always dilated. According to Radonic et al. the use of Z-scores, as recommended in the Ghent II criteria, may therefore lead to the diagnosis of Marfan syndrome being missed in patients with a large BSA.

A 1993 study of 182 tall men and women showed that the aortic root diameter does not increase linearly with a length of >P95, and that the aortic root diameter no longer increases with a larger BSA. The P95 does not exceed 39 mm (Reed et al., 1993). Kinoshita et al. (2000) investigated the prevalence of aortic dilatation amongst 1,929 athletes (particularly basketball players) and also found that the relationship between aortic root diameter in relation to the BSA does not increase linearly. The measured P95 was smaller than 39 mm. They considered an aortic root of >40 mm to be pathological and this was confirmed in 7 of the 1,929 athletes, including two for whom a diagnosis of Marfan syndrome was established. All other measurements were <40 mm.

In children, the measured dimensions are normally expressed as Z-scores. Standardisation by body surface is common, although the aortic root dimensions also seem to show a good correlation with height (Sheil et al., 1995). Separate nomograms have also been developed for tall children and adolescents, adapted to the specific build of this group (Rozendaal et al., 1998).

The nomograms for children recently published by Gautier and by Pettersen are based on

measurements in larger groups of children than the original Roman nomograms (353 or 782 versus 53) (Gautier et al., 2010; Pettersen et al., 2008). The Roman and Gautier nomograms were developed from leading edge to leading edge measurements in diastole, in accordance with the guidelines for adults from the American Society of Echocardiography. The Pettersen nomograms are based on inner edge to inner edge measurements in systole, in accordance with paediatric guidelines. Z-scores can easily be calculated using www.parameterz.blogspot.com or via www.marfan.org.

Conclusions

Level 4	Guidelines for adults and children recommend that ultrasound examination of the aortic root in patients suspect for Marfan syndrome measure in the parasternal long-axis view. Diameters are measured at the level of the aortic annulus, aortic root, ST junction and at the ascending aorta, one centimeter above the ST junction. D Lang et al., 2005; Lopez et al., 2010
Level 3	Literature cites various cut-off values for determining aortic root dilatation in adults with normal stature, with an aortic root diameter greater than 40 mm usually considered as abnormal. Depending on age and BSA, smaller diameters can already be considered abnormal. C Biaggi et al., 2009; Pellicia etl, 2010; Radonic et al., 2011; Kinoshita et al., 2000
Level 4	Most of the normal values for echocardiography in adults quoted in the literature are based on leading edge to leading edge measurements in diastole. D Lang et al., 2005; Roman et al., 1989
Level 4	Ultrasonography in children generally utilises Z scores for the expression of measured dimensions. Published nomograms specific for children are based on different methods of measurement. D Lopez et al., 2010; Gautier et al., 2010; Pettersen, 2008

Level 4	Specific nomograms have been developed for ultrasound measurements of aortic root dimensions in tall children and adolescents. D Rozendaal et al., 1998

Considerations

Aortic root Z-scores have a central role in the Ghent II criteria. In addition to the determination of the absolute diameter, it can sometimes also be useful to express the measured aortic root diameter as a standardised Z-score using one of the published nomograms, under the condition that the method of measurement corresponds to that of the nomogram. However, the Z-score is unreliable in patients with a large body surface area (>2 m^2), such as is often the case in Marfan syndrome (Radonic et al., 2011).
In the opinion of the working group, an aortic root diameter of >40 mm is always dilated, although this figure may still fall within the norm on the extrapolated data in the Roman nomograms. In individuals with a normal posture, the aortic root is usually smaller than 38 mm. When in doubt as to a dilatation, the form of the aortic root (pear shape) and the relation of the aortic root to the immediate area, left atrium and ascending aorta may help to confirm the diagnosis of aortic root dilatation.

The three sinuses of Valsalva can be visualised in the parasternal long -axis view. In cases of aortic root dilatation, a typical cloverleaf shape is seen, which is sometimes accompanied by an asymmetric dilatation of the sinus of Valsalva. This can mean that the diameter in the long-axisview may not be the maximal diameter.

Imaging the aorta with cardiovascular MRI (CMR) and/or CT
The entire aorta can be visualised using magnetic resonance techniques. This is especially important for adult Marfan patients because aortic dilatation can also occur beyond the aortic root in the distal aorta, especially following aortic root replacement and with increasing age. In adult Marfan patients, the entire aorta should therefore be visualised with MRI as soon as the diagnosis is made. The frequency of follow-up MRI depends on the conditions at baseline. In young children, the entire aorta can usually be clearly visualised using ultrasound, in addition to the fact that widening of the distal aorta occurs only rarely in young children. MRI is performed in this age group as indicated.
General MRI guidelines indicate that the aortic root should be measured on triggered

MR images in the short axis, from leading edge to leading edge. Magnetic resonance angiography (MRA) is not reliable when measuring the aortic root diameter because only the aortic lumen is depicted.
MRI is preferred for routine assessment of (young) adults. The advantage of MRI is that any cross-sectional plane can be chosen, allowing the aortic diameter to be measured in the longitudinal plane. This can be of importance in aortas with considerable tortuosity. In addition, radiation exposure and the administration of contrast agents is avoided.
For the frequency of surveillance, please refer to section 10.

Postoperative assessment
Because the chosen projection surfaces of consecutive MRI tests are not always exactly the same, an increase in the diameter of the aorta can sometimes be better assessed with CT scans. The CT scan is preferred for postoperative assessment in some clinics for this reason (for example, after a type A dissection or for following the growth of the descending aorta in the case of a persistent type B dissection). The possible development of pseudo-aneurysms after surgery can be determined at an early stage using CT. MRI is preferred where a patient shows a contrast allergy.

Recommendations

Perform ultrasound aortic measurements at 4 levels in the 2D parasternal long-axis perpendicular to the direction of blood flow, with the aim of visualising the maximum diameter of the aortic root. Also evaluate the asymmetry of the root in the short axis. Carefully asses the largest diameter at follow-up.

For adults, in the context of standardisation, follow the guidelines of the American Society of Echocardiography, with the ultrasonographic measurements in diastolic stop-frame, from leading edge to leading edge.

In an adult, an aortic root diameter of more than 40 mm should generally be regarded as dilated. In the assessment of aortic root diameter, always take into account the age, sex and BSA of the patient, and depending on these factors, smaller diameters may already be considered abnormal. The use of a Z-score may be helpful in these cases.

In children, express the values obtained by ultrasound in Z-scores, using published nomograms or digital formulas. Document the measurement technique and the matching nomograms used.

Image the entire aorta in adult Marfan patients with MRI once the diagnosis is established.
The frequency of follow-up MRIs depends on the conditions at baseline.

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Section 5 Differential Diagnosis

Introduction

The diagnosis of Marfan syndrome is based on internationally agreed criteria. The latest criteria were published in July 2010 (Loeys et al., 2010; Dietz et al., 1993).
A diagnosis of Marfan syndrome is based on a combination of cardiovascular, ophthalmic, and systemic (including skeletal) characteristics, together with molecular analysis.
These 'revised Ghent criteria' (Ghent II criteria) are still under discussion and no consensus has yet been reached.

Since no individual symptom is specific for Marfan syndrome, other diagnoses should always be considered. This also applies for individuals with Marfan syndrome, in whom no pathogenic *FBN1* mutation has been found. The Ghent II criteria incorporate the criteria for Ectopia Lentis syndrome (ELS), Myopia-Mitral valve prolapse-borderline and non-progressive Aortic root dilatation-Skeletal Findings-Striae (MASS) and Mitral Valve Prolapse Syndrome (MVPs) (see Table 5.1). In addition, in cases of ectopia lentis with aortic root dilatation or aortic root dilatation with a high systemic score, indications for other syndromes must be absent in order to establish a diagnosis of Marfan syndrome.
This distinction is also clinically important because the different diagnoses all have differing inheritance, prognosis and needs for guidance. Knowledge of differential diagnostic considerations is therefore essential.

Summary of the literature

Describing the medical conditions that must be considered in a differential diagnosis required an alternative literature search, because the scientific justification of this aspect is less relevant.
Table 5.1 has been prepared on the basis of two core articles, Loeys et al. (2010) and Dietz et al. (1993), and the first column includes the characteristics of Marfan syndrome. In addition, the specific characteristics of the other syndromes are described (and core articles were sought on these syndromes). Genereviews.org was frequently consulted (also available via Pubmed).
The table attempts to provide a summary of the alternative diagnoses for the main features of Marfan syndrome, ectopia lentis and aortic root dilatation. Since most referrals

to a Marfan clinic – including the question of presence or absence of Marfan syndrome - are based on the existence of an aortic root dilatation or dissection, ectopia lentis and distinctive habitus (usually tall stature), marfanoïde habitus is also included as an entry in the table, with its specific differential diagnosis. The characteristics appropriate to Marfan syndrome are in regular letters. Characteristics in in italics are appropriate to (one of the) differential diagnoses. The presence of a characteristic in italics indicates that the diagnosis of Marfan syndrome needs to be reconsidered.

The characteristics of each syndrome are classified as possibly overlapping with Marfan syndrome, or specific for the syndrome.

Ectopia Lentis syndrome (ELS) (Ades et al., 2004; Aragon-Martin et al., 2010)
Autosomal dominant and recessive inheritance (dominant: sometimes *FBN1*, which is not associated with aortic root dilatation / recessive: *LTBP2* and *ADAMTSL4* mutations).
Overlapping features: lens luxation, skeletal features.
Specific characteristics: none, the lens luxation is usually bilateral and congenital, without ectopia pupillae. N.B. Whether there is a long term risk of aortic root dilatation in the event of a *FBN1* mutation is unclear.

Myopia-Mitral valve prolapse-borderline and non-progressive Aortic root dilatation-Skeletal findings-Striae (MASS) (Loeys et al., 2010)
Autosomal dominant inheritance.
Overlapping features: Myopia, **M**itral valve prolapse, borderline and non-progressive **A**ortic root dilatation, **S**kin and **S**keletal features.
Specific characteristics: none.

Mitralis valve prolapse syndrome (MVPS) (Loeys et al., 2010)
Autosomal dominant inheritance.
Overlapping features: mitral valve prolapse, (subtle) skeletal features.
Specific characteristics: none.
Shprintzen Goldberg syndrome (SGS) (Greally, 2010)
Inheritance uncertain (a few *FBN1* or *TGFBR2* mutations described).
Overlapping features: phenotype: dolichostenomelia, arachnodactyly, pectus, scoliosis, aortic root dilatation (rarely), high palate.
Specific characteristics: Craniosynostosis, mental retardation, Chiari malformation, hypertelorism, proptosis, rib anomalies, clubfoot.

Table 5.1. Differential diagnostic considerations - Marfan syndrome

	Marfan	ELS	MASS	MVPS	SGS	LDS	AOS	CCA	FTAAD	WMS	EDS-CT	EDS HT	EDS-VT	EDS -KST	HHC	Stickler	FraX	Lujan-Fryns	AT	Cutis Laxa
Aortic dilatation and/or dissection											&	&								
Ectopia lentis																				
Marfanoid habitus^ (tall stature, long legs)																				
Mitral valve prolapse																				
Skeletal features#	all			pe, sc, ar	pe, sc, ar	pe, sc, ar, pl	pe, Sc, ar, pl	sc, ar						sc	pe, sc					pe, ar
Myopia																				
Facial features*	all				d											m		m		m, r
Skin abnormalities®																				
Contractures																				
Hypermobility																				
Craniosynostosis																				
Developmental delay																				
Chiari malformation																				
Rib abnormalities																				
Clubfoot																				
Hypertelorism																				
Bifid uvula/ cleft palate																				
Blue sclerae																				
Arterial tortuosity																				
Organ rupture																				
Thrombosis																				
Hearing problems																				
Skelet dysplasia/arthritis																				

ELS : Ectopia Lentis Syndrome
MASS : Myopia, Mitral valve prolapse, borderline Aortic root dilatation, Striae, Skeletal features
MVPS : Mitral Valve Prolapse syndrome
SGS : Sprintzen-Goldberg syndrome
AOS : Aneurysms-Osteoarthritis syndrome
LDS : Loeys-Dietz syndrome
CCA : Congenital Contractural Arachnodactyly
FTAAD : Familial Thoracic Aorta Aneurysms and Dissections
WMS : Weill-Marchesani syndrome
EDS-CT : Ehlers-Danlos Syndrome, classic type
EDS-HT : Ehlers-Danlos Syndrome, hypermobile type
EDS-VT : Ehlers-Danlos Syndrome, vascular type
EDS-KST : Ehlers-Danlos Syndrome, kyphoscoliosis type
FraX : Fragile-X syndrome
HHC : Hyperhomocysteinuria
AT : Arterial Tortuositas

^ Also consider MEN2B, Cohen, and certain genes involved in X-linked mental retardation (SMS, ZDHHC9)
* facial features: d=dolichocephaly, e=enophthalmos, pf=downslant palpebral fissures, m=malar hypoplasia, r=retrognathia
# Skeletal features: wt=wrist/thumb sign, pe=pectus, pl=pes planus, sc=scoliosis/kyphosis, ar=arachnodactyly
& McDonnell et al. (2006) described a mildly dilated aortic root in the classic and hypermobility type EDS patients; however, the cohort was small, aortic diameters were not normalised to BSA, and Marfan syndrome cannot be excluded in patients with aortic root dilatation. Furthermore, this publication seems to be the only one in which an aortic root dilatation is described.

Dark grey: frequent/pronounced.
Light grey: less frequent/less pronounced.

Loeys-Dietz syndrome (LDS) (Loeys & Dietz, 2008)

Type 1

Autosomal dominant inheritance (mutations in *TGFBR1*, *TGFBR2*).

Overlapping features: long face, downward slanting palpebral fissures, high palate, malar hypoplasia, micrognatie, retrognathism, pectus, scoliosis, arachnodactyly, hypermobility, dural ectasia, aortic root dilatation or dissection.

Specific characteristics: hypertelorism, broad or bifid uvula, cleft palate, learning disabilities, hydrocephalus, chiari malformation, blue sclerae, exotropia, craniosynostosis, cervical spine instability, club foot, soft pasty skin, translucent skin, easy bruising, generalised arterial tortuosity and aneurysms and/or dissection.

Type 2 (formerly: Marfan syndrome type 2)

Autosomal dominant inheritance (mutations *TGFBR1*, *TGFBR2*).

Absent LDS type 1 characteristics: arterial tortuosity and almost all other characteristics except aneurysms and/or dissection of aorta and other arteries.

Features overlapping with Marfan syndrome: sometimes marfanoid habitus and arachnodactyly.

Absent Marfa features: ectopia lentis.

Aneurysms-Osteoarhritis syndrome (van de Laar et al. 2011)

Autosomal dominant inheritance (mutations *SMAD3*)

Features overlapping with Marfan syndrome: aortic dilatation or dissection, mitral valve prolapse, hypermobility, marfanoid habitus, pectus deformities, scoliosis

Specific characteristics: hypertelorism, cleft palate/uvula, explicit osteoarthritis

Congenital Contractures and Arachnodactyly (Godfrey, 2012)

Autosomal dominant inheritance (heterozygous mutations in *FBN2*).

Overlapping features: long, thin fingers and toes, kyphosis, scoliosis, aortic root dilatation (occasionally).

Specific characteristics: ear abnormalities ("crumpled ears", "folded upper helix"), contractures of knees and ankles, flexion contracture at the proximal interphalangeal joints of fingers and toes, hip contractures, adducted thumbs, clubfeet, muscle hypoplasia.

(Familial) thoracic aortic aneurysms and dissections ([F] TAAD) (Milewicz & Regalado 2012)

Autosomal dominant inheritance (mutations in *MYH11*, *ACTA2*, *TGFBR1*/2, *Smad3*, *MyLK* and as yet undiscovered genes). (F)TAAD associated with mutations in *TBFBR1/2* without features of LDS is sometimes called LDS type 2 or Marfan syndrome type 2.

Overlapping features: aortic dilatation (but usually of the ascending aorta and not of the aortic root).

Specific characteristics: none.

Weill-Marchesani syndrooem (WMS) (Tsilou & MacDonald, 2007)

Autosomal dominant and recessive inheritance (*ADAMTS10* mutations).

Overlapping features: lens luxation, myopia, contractures.

Specific characteristics: small stature, microspherophakia, brachydactyly.

Ehlers-Danlos syndrome (EDS) classical type, type 1 (Malfait et al., 2011)

Autosomal dominant inheritance (mutations in *COL5A1, COL5A2*).

Overlapping features: hypermobility (more pronounced in EDS).

Specific characteristics: hyperelastic skin, abnormal wound healing, soft pasty skin.

EDS hypermobile type, type III (Levy, 2010)

Autosomal dominant inheritance.

Overlapping features: hypermobility.

Specific characteristics: None; there is overlap with familial and physiological hypermobility.

EDS vascular type, type IV (Pepin & Byers 2011)

Autosomal dominant inheritance (*COL3A1* mutations).

Overlapping features: hypermobility (limited to distal finger joints), Ao aneurysm/dissection.

Specific characteristics: thin skin (dark under the eyes), easy bruising, wide dystrophic scars; Facial: prominent eyes, sharp facial features, organ ruptures, artery dilatation/dissection, especially abdominal aorta (generalised).

Absent Marfan characteristics: Marfanoid habitus.

EDS kyphoscoliotic type, Type VI (Yeowell et al., 2008)

Autosomal recessive inheritance (mutations in *PLOD1*, *CHST14*).

Overlapping features: kyphoscoliosis, hypermobility, hypotonia, sometimes eye problems (sclerae weakness with globe rupture, myopia), MVP.

Specific characteristics: rupture of medium-sized arteries.

Homocysteinuria (HHC) (Picker & Levy, 2011)

Autosomal recessive inheritance (mutations in *CBS*).

Overlapping features: myopia, ectopia lentis, skeletal abnormalities, physique, pectus excavatum/carinatum, scoliosis, mitral valve prolapse, high palate, inguinal hernia.

Specific characteristics: mental retardation, intravascular thrombosis, thromboembolism.

Stickler syndrome (Robin et al., 2011)
Autosomal recessive inheritance (mutations in *COL2A1*, *COL11A1*, *COL11A2*).
Overlapping features: myopia, retinal detachment, mid-face hypoplasia.
Specific characteristics: hearing loss, cleft palate, spondyloepiphyseal dysplasia, premature arthritis, congenital abnormality of vitreous humor.

Fragile X syndrome (Saul & Tarleton, 2012)
Sex-linked inheritance (*FMR1* mutations).
Overlapping features: long face, hypermobility.
Specific characteristics: mild/moderate mental retardation, large head, prominent forehead and chin, large ears, large testes, behavioural problems.

Lujan-Fryns syndrome (van Buggenhout & Fryns, 2006)
Sex-linked inheritance, especially reflected in men.
Overlapping features: long narrow face, maxillary hypoplasia, small mandible, tall stature, marfanoid habitus.
Specific characteristics: prominent forehead, mental retardation, behavioural problems.

Arterial Tortuosity (Canadas et al., 2010; Callewaert et al., 2008)
Autosomal dominant inheritance (mutations *GLUT10*).
Overlapping features: long face, dilated arteries and aorta, hypermobility.
Specific characteristics: tortuosity of aorta and large arteries.

Cutis Laxa (Loeys B, 2011 ; Callewaert et al., 2012)
Autosomal recessive inheritance (mutations *FBNL4/EFEMP2*), autosomal dominant inheritance (mutaties *ELN*)
Overlapping features: aorta aneurysms, hypermoblity, retrognatia, arachnodactyly, pectus deformity, malar hypoplasia, high arched palate.
Specific characteristics: skin phenotype, arterial tortuosity, lung emphysema.

Recommendation

Consider other diagnoses, if a feature not matching Marfan syndrome is present (as in Table 5.1)

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Section 6 Treatment of Skeletal Abnormalities

Introduction

Abnormalities of the musculoskeletal system are often present in patients with Marfan syndrome. The most common problems are:

- Scoliosis;
- Spondylolisthesis;
- Pectus excavatum/pectus carinatum;
- Instability (multidirectional) of the shoulder;
- Instability carpometacarpal (CMC) joint 1;
- Protrusio Acetabuli;
- Patellar instability;
- Pes planovalgus;
- Hammer-/claw toes.

The question is whether the treatment of skeletal abnormalities in Marfan patients is different from that in patients without Marfan syndrome.

Summary of the literature

Scoliosis

Scoliosis is a common orthopaedic problem in patients with Marfan syndrome. A scoliosis is present in approximately 62% of patients, where a curve greater than 40° suggests a high probability of progression following skeletal maturation (Sponseller et al., 1995). The curves are noticeably more rigid in comparison with idiopathic scoliosis, which may mean that the probability of success of brace treatment is lower.

A brace is the only non-invasive method available to counter the progression of scoliosis. Because the use of a brace has a significant impact on the life of a patient, it is important to be able to reach a judgement on the effect of the treatment.

In idiopathic scoliosis, brace treatment is known to be more favourable than the natural course in patients with a curve of between 20 and 45 degrees whose skeleton is still immature (Risserstadium less than or equal to 2). In 60-80% of cases the curve increases by less than 5 degrees during the treatment, which often allows an operation to be avoided (Emans et al., 1986; Nachemson & Peterson, 1995; Rowe et al., 1997).

Only 2 retrospective studies describe the treatment of scoliosis in Marfan patients. Sponseller et al. (2000) have show that the effect of a Boston brace is limited. Of the 24 patients (demonstrated Marfan syndrome, curve of 20-45°, Risser 0-2 at the beginning of brace treatment), 22 could persist with the brace program, the remaining two being unable to tolerate wearing the brace. The patients were followed for at least two years (until skeletal maturation or surgery), and during follow-up 4 of the 24 patients (17%) were found to have a curve increase of less than 5 degrees and a curve of less than 45 degrees. Fifteen patients underwent a surgical intervention and the remaining 5 were indicated for surgery but an operation had not yet been carried out.
Birch & Herring (1987) treated eight Marfan patients (diagnosis based on clinical signs, no DNA test) with a Boston or Milwaukee brace and saw a stabilisation of the curve in 1 patient. She was already three months postmenarcheal, however. Six were surgically treated following curve progression, and one patient refused surgery (Birch & Herring, 1987).

Spondylolisthesis

There is evidence that the incidence of spondylolisthesis occurrence and the severity of the slip are slightly higher than in patients without Marfan syndrome (Sponseller et al., 1995). There is no evidence that treatment differs from that of patients without Marfan syndrome.

Pectus excavatum

There is no evidence in the literature that there are grounds to treat Marfan patients with pectus excavatum differently from non-Marfan patients, nor regarding the indication for surgery, nor regarding the timing of any surgical correction.

Other abnormalities

No literature was found to indicate that treatment should depart from the standard treatment applicable to the abnormalities mentioned in the introduction in patients without Marfan syndrome.

Conclusions

Level 3	There are indications that, in Marfan patients with a still immature skeleton (Risser 2 or less) and scoliosis curves of between 20 and 45 degrees, wearing a brace can avoid the need for surgery in a small proportion of patients. *C* Sponseller et al., 2000; Birch & Herring, 1987
Level 3	There are indications that the percentage of patients in whom a brace can prevent surgery is lower in Marfan than in non-Marfan patients. *C* Sponseller et al. 2000; Birch & Herring, 1987
Level 4	There is insufficient available literature to justify treating other skeletal abnormalities in Marfan syndrome differently to those in patients without Marfan syndrome. *D* Opinion of the working group

Considerations

Studies on the effects of wearing a brace do not clarify the issue of whether, without the brace, the scoliosis would have progressed to the extent to make surgery unavoidable. In other words, whether the brace affects the natural course of the disease. Adequate consideration of the advantages and disadvantages of both wearing a brace and of surgery should therefore always include the patient and possibly also the parents.

In cases of pectus excavatum, an indication for surgery is based on the psychological problems of a patient with this deformity. These problems usually start around adolescence, and do not differ between Marfan patients and non-Marfan patients.

There is no evidence in the literature for grounds to treat Marfan patients with pectus excavatum differently to non-Marfan patients, neither regarding the indication for surgery, nor regarding the timing of a possible surgical correction (Scherer et al., 1988; Jaroszewski et al., 2011).

Although improvements in cardiac and pulmonary function are mentioned in the literature, this phenomenon long remained difficult to objectify (Morshuis et al., 1994). This effect

was attributed to an improved confidence and thus greater participation in gymnastics, sports, etc. post-correction. More recently, there are some indications for a measurable improvement in exercise capacity following surgical correction of severe pectus excavatum (Malek et al., 2006). There also seems to be no difference between patients with Marfan syndrome and patients with other diseases on this specific issue.
There are also no differences between Marfan syndrome and non-Marfan patients with regard to the use of surgical techniques.

Publications on combined correction of the chest wall deformity and cardiac surgery (e.g. aortic root replacement) are limited to case reports.

It is important to realise that cardiac surgery is no longer possible following insertion of a Nuss bar. Prior to insertion of a Nuss bar, evaluation by a (child) cardiologist is recommended to evaluate the risk of cardiac surgery during the period the Nuss bar is in situ.

The working group is of the opinion that the musculoskeletal abnormalities found in Marfan patients should be treated in the same manner as in patients without Marfan syndrome. The treatment must be performed by a surgeon with specific experience in the area in question.

Recommendations

In general, treat abnormalities of the musculoskeletal system in patients with Marfan syndrome in the same manner as for patients without Marfan syndrome.

In Marfan patients with scoliosis of between 20 and 45 degrees and a still immature skeleton, the (low) expected success rate of a brace should be weighed against the discomfort and the advantages and disadvantages of an operation.

Consult a (child) cardiologist before insertion of a Nuss bar.

Problems with the musculoskeletal system in patients with Marfan syndrome should be treated by a specialist with experience in the field of the specific musculoskeletal problem. It is not necessary that this occur within a Marfan team.

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Section 7 Drug Treatment

Introduction

Current drug treatment in Marfan syndrome is focused on slowing aortic root dilatation through a reduction in the haemodynamic stress in the aorta, mainly by means of beta-blockers. However, there is increasing evidence that the renin-angiotensin system (RAAS) plays a role in the development of aneurysms. Blockade of the RAAS system not only lowers blood pressure, but also intervenes in the molecular mechanisms underlying the development of aneurysms, such as the TGFβ cascade and the so-called extracellular-signal-regulated kinases (ERKs).

Summary of the literature

The first open-label, randomised study of the effect of drug treatment in Marfan patients was published in 1994 (Shores et al., 1994), in which 70 Marfan patients aged between 12 and 50 years were treated with the beta blocker, propranolol. After 4 years of follow-up, the treatment group had a 73% lower rate of aortic root dilatation and a lower mortality. Mechanical effects of beta-blockade were considered to be the cause of the beneficial effect of beta blockers. Lowering of blood pressure and a decreased contractility of the left ventricle lead to a reduction in haemodynamic stress in the aorta. Although the utility of beta blockers was never conclusively proven in a prospective double-blind, randomised study, the use of beta-blockade is currently the standard treatment in patients with Marfan syndrome and is recommended in all guidelines (Baumgartner et al., 2010; Hiratzka, 2010; Silversides et al., 2010; Regitz-Zagrosek et al., 2011).

The cystic medial degeneration in the aortic wall seen in aneurysms is accompanied by apoptosis and loss of smooth muscle cells, degeneration of elastic fibres and build-up of proteoglycan, a major constituent of the extracellular matrix. Angiotensin II contributes to this process via angiotensin II type 1 or 2 (AT1- en/of AT2-) receptors. In recent years, a number of studies have been published on the effect of various antihypertensive drugs, and two small studies have compared the effect of ACE inhibitors and beta-blockers. ACE inhibitors were more effective in reducing arterial stiffness, improving aortic distensibility and delaying the growth of the aorta, compared to beta blockers (Ahimastos, 2007; Yetman, 2005).

In 2006, the AT1 receptor blocker Losartan was shown to have a beneficial effect on the structure of the aortic wall and on aortic growth in mice with a *FBN1* mutation (Habashi

& Loeys, 2006). In a small retrospective cohort study in 18 children with a severe form of Marfan syndrome and rapid aortic growth, an AT1 blocker was added to existing medication and the growth of the aorta was followed for 12-47 months. A significant slowing of aortic growth was seen following treatment with Losartan, after adjusting for age and BSA (Brooke et al., 2008).

The prophylactic use of beta blockers in children with Marfan syndrome is still a subject of discussion. Most published studies persist in enrolling only a small number of children, thus preventing a conclusive appraisal of the effect of beta-blockers in children with Marfan syndrome. In a retrospective study by Selamet Tierney (2007) of 63 children with Marfan syndrome, up to 18 years old, the beneficial effect of beta-blockers on the speed of aortic root dilatation could not be demonstrated after 6 years of follow-up (Selamet Tierney, 2007). The retrospective design, with a possible selection bias, and the small numbers make it impossible to draw definitive conclusions. In contrast, a similar retrospective study by Ladouceur et al. (2007) of 115 children younger than 12 years, including 77 treated with beta blockade, could show a decrease in the rate of aortic root dilatation of 0.16 mm/year in the treated group compared to the non-treated group (Ladouceur et al., 2007). The authors concluded that it is advisable to start beta blockade at the moment of diagnosis, but because the treated group had greater aortic root dilatation than the non-treated group, a selection bias seems plausible.

Conclusions

Level 3	There are indications for an inhibitory effect of beta blockers on the growth of the aortic diameter in Marfan patients over the age of 12. B Shores et al., 1994 D Baumgartner et al., 2010; Hiratzka, 2010; Silversides et al., 2010; Regitz-Zagrosek et al., 2011
Level 2	Results regarding the effect of beta-blockers on aortic growth in children are contradictory. B Selamet Tierney, 2007; Ladouceur et al., 2007
Level 3	There are indications that Losartan slows aortic root growth in children with Marfan syndrome. C Brooke et al., 2008

Considerations

Although the study by Brooke suggests that Losartan may have a beneficial effect on aorta growth, this beneficial effect should be confirmed through prospective randomised trials before definitive conclusions are drawn. Several trials, with a number of variations in the design, are currently underway worldwide. Until evidence regarding the effects of Losartan on the course of Marfan syndrome becomes available, a conservative approach to the administation of Losartan is appropriate.
Other potentially beneficial drugs, such as doxycycline (Chung, 2008) and pravastatin, are currently being investigated in mouse models.

Beta-blockers may have side-effects such as bronchospasm, fatigue, depression, insomnia and behavioural problems. These side-effects are especially unacceptable in children considering that the efficacy of these drugs on the inhibition of aortic growth is not conclusively proven.
Because a recommendation regarding the prophylactic use of beta-blockers in children with Marfan syndrome is lacking in current international guidelines, it seems sensible to carefully weigh the advantages and disadvantages of the use of beta-blockers for individual patients, and not to routinely prescribe these drugs. It is common practice in the Netherlands to prescribe beta blockers for children with evident aortic root dilatation.
The use of Losartan in children with Marfan syndrome is uncommon in the Netherlands. Furthermore, Losartan is not registered in the Netherlands as a hypotensive agent in children <6 years. Because the effect of Losartan on the course of Marfan syndrome is unproven, caution should be exercised when considering prescribing Losartan to children.

Recommendations

Prophylactic use of beta blockers should be continued in adult patients with Marfan syndrome, for the time being.

Do not routinely prescribe beta blockers to children with Marfan syndrome, but carefully weigh the advantages and disadvantages on an individual basis. It is customary to prescribe beta-blockers in children with evident aortic root dilatation.

Be conservative in the prescription of Losartan to children at present.

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Section 8 Timing of Aortic Surgery in Adults

Introduction

An aortic dissection or symptomatic aortic aneurysm is a potentially life-threatening condition. The risk of rupture is strongly dependent on the diameter, and an aneurysm with a diameter of >60 mm has a 25 times higher chance of rupture than when the diameter of the aneurysm is between 40 and 49 mm (Davies et al., 2002). A decision to operate is always a trade-off between the risk of rupture and the surgical risk. Elective surgery of the descending aorta carries a high risk of morbidity and a somewhat lesser risk of mortality (10.9%) (Davies et al., 2002), but it is still much lower than under emergency conditions. In contrast, elective surgery of the ascending aorta (and arch) has low mortality (2.5%) and morbidity, especially in centers with extensive experience in this area (Davies et al., 2002). This surgical risk is accepted in the light of a greatly improved life expectancy after surgery.

The diameter of the aorta is measured in various ways (see also text on diagnostic imaging). The surgical literature generally describes a CT examination that uses the internal diameter (inside wall to inside wall), while the cardiological literature often describes ultrasound, with the so-called 'leading edge to leading edge' method (front wall to front wall; thus including measurement of a single wall thickness). Unless otherwise expressly stated, the diameters of the aorta given below refer to the internal diameters.

Summary of the literature

Most articles focus on small groups of patients and do not focus specifically on the Marfan population. Randomised studies are generally lacking, and prospective studies are rare and usually contain small numbers of patients. The recommendations of the working group are largely based on U.S. (Hiratzka 2010) and European (Baumgartner et al., 2010) guidelines, which include the most relevant literature.

Asymptomatic aortic root and/or ascending aorta dilatation:
The most recently published American guidelines for the diagnosis and treatment of patients with thoracic aortic pathology propose referral of Marfan patients for elective surgical replacement of the aortic root and/or ascending aorta when the internal diameter is >45 mm (corresponding with an external diameter of ≥50 mm) (Hiratzka et al., 2010; Pearson et al., 2008).

A surgical correction is also considered indicated when the aortic root and/or ascending aorta has an internal diameter of <45 mm, in combination with:

- A rapid increase in the diameter (defined as >5 mm per year), and/or;
- A family history of aortic dissections and/or;
- A serious aortic regurgitation;
- Desire for pregnancy.

The European guideline (Baumgartner et al., 2010) also cites an upper limit of 50 mm (leading edge to leading edge) as an absolute indication and 45 mm when combined with the above mentioned risk factors.
The cited values are approximately 5 mm lower than in the non-Marfan patients.

Asymptomatic dilatation of the aortic arch, descending aorta or thoraco-abdominal aorta:
In the case of these patients, a diameter of 55 mm or larger is an indication for surgical intervention. In the case of rapid growth (>5 mm per year), a family history of dissections or a wish to become pregnant, an indication for surgical correction is usually given for a diameter of 50 mm or even for 45 mm (Hiratzka et al., 2010). This was supported by a recent study, specifically of Marfan patients, which showed a significant increase in the risk of rupture or dissection with a diameter 50 mm or more (Jondeau et al., 2012).

Symptomatic aortic dilatation:
As is the case with non-Marfan syndrome patients, a surgical correction with optimal medical treatment is always indicated for symptomatic aortic dilatation (Hiratzka et al., 2010), especially if a slow response to intravenous antihypertensive treatment is seen. If dilatation of the aorta is not clearly established, a plausible connection between the symptoms and aortic pathology should be confirmed.

Acute dissection type A:
All patients with an acute type A dissection (Stanford classification type A, DeBakey classification type I and II) have an absolute indication for emergency surgery (Hiratzka, 2010), whether or not he or she has Marfan syndrome.
N.B. An intramural haematoma should be treated as an acute dissection (Hiratzka et al., 2010).

Acute dissection type B:
The literature on the management of patients with acute type B dissection (Stanford classification type B; DeBakey classification types I and III) was inconclusive for some years. Experience with the placement of an endoprosthesis during the acute phase has remained

limited, due to an apparent association with high morbidity and mortality. Partly based on these experiences, and in accordance with current opinion, the generally recommended policies are:
A conservative policy, together with optimal drug treatment (including intravenous antihypertensive treatment), is recommended for uncomplicated dissections (i.e. without ischemia of the end organs, without leakage from the false lumen and without uncontrolled hypertension or persistent pain). The morbidity and mortality of surgical correction (open or endovascular) is high in the acute phase of the dissection, and is therefore only justified in the case of complications (Hiratzka et al., 2010).

Chronic dissection:
Indications for a patient with a chronic dissection are as applied for dilatation of the aorta (q.v.) (Hiratzka et al., 2010).

Considerations

The increased risk of rupture or dissection at larger aortic diameters and associated risks (including death), versus the risks of elective surgery, mean that the above recommendations from international guidelines are taken as standard despite the low level of evidence.

Individuals with a smaller body surface area (BSA) usually have a smaller aortic diameter. In general, the aortic root diameter in women is 5 mm smaller than in men (in part due to a smaller BSA). Recommendations should be applied using common sense. This means that the indication for surgery may be somewhat more aggressive in patients with a smaller BSA and more conservative in patients with an extremely high BSA.

Some remarks concerning surgical procedures:
In experienced centers, a valve-sparing procedure for the surgical correction of aortic root aneurysm or a type A dissection is usually possible, and this procedure should always be given preference. Referral to a center with experience in valve-sparing surgery is therefore recommended in cases of elective surgery. Due to an ongoing risk of annular dilatation in patients with Marfan syndrome, this procedure should not employ the remodelling technique (as Yacoub) but a modified reimplantation technique (as David) (Hiratzka et al., 2010; Kallenbach et al., 2007) .
The use of an endoprosthesis for aneurysms of the descending aorta is not yet recommended in patients with Marfan syndrome (Nordon et al., 2009). This is related to

an expectation of further aortic dilatation and the possibility of a type I or type V endoleak, an indication for a secondary procedure.

If a patient is scheduled to undergo cardiac surgery for another reason, for example, mitral regurgitation, a replacement may be considered even in cases with a less strongly dilated ascending aorta. An additional argument is the fact that damage to the aorta (aortic cannula, aortic root cannula and aortic clamp) could be a trigger for a dissection in cases with poor tissue quality.

Recommendations

Indications for elective surgical replacement of the aortic root and/or ascending aorta in asymptomatic Marfan patients occur at diameters of >45 mm on CT (internal diameter) or > 50 mm on ultrasound or MRI (leading edge to leading edge). Indications for surgery (some mm's) are earlier in case of:
- a rapid increase in the diameter (>5 mm per year), and/or;
- a family history of aortic dissection and/or;
- a major aortic regurgitation;
- desire for pregnancy.

Proceed with replacement if a patient has to undergo heart surgery for any other reason, even in cases with a lesser dilatation of the aortic root and/or ascending aorta.

Consider a diameter of 55 mm or larger as an indication for surgical intervention in asymptomatic Marfan patients with dilatation of the aortic arch, descending or thoracoabdominal aorta. Indicate surgical correction at a diameter of 50 mm or even 45 mm in case of rapid growth (> 5 mm per year), family history of dissections or a wish to become pregnant.

A surgical correction with optimal medication is indicated for all patients with symptomatic aortic dilatation, especially if a slow response to intravenous antihypertensive treatment is seen.

An acute type A dissection is an absolute indication for emergency surgery. Uncomplicated acute type B dissections are handled conservatively using optimal drug treatment. Surgical correction during the acute phase of a dissection carries a high risk and it is therefore only justified in the case of complications.

Apply indications for a patient with a chronic dissection as for dilatation of the aorta.

For surveillance following cardiac surgery, see section 10.

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Section 9 Timing of Aortic Surgery in Children

Introduction

While in adults the discussion on the optimal moment for aortic surgery centers around the question of at what absolute aortic root diameter is the probability of dissection or rupture so high that preventive aortic root replacement is justified, in the case of a growing child criteria are sought that can be related to physical proportions (weight, height, body surface area).
Aortic dissection is extremely rare under the age of 10 (Gillinov et al., 1997) or 12 (Zanotti et al., 2008). This means that preventive aortic root replacement is not indicated in young children. Because dissection is rare in children younger than 12 years, regardless of the degree of aortic root dilatation, Zanotti et al. (2008) are of the opinion that the use of z-scores as an indicator for surgery is unnecessary. This view is also expressed in a recent article (Everitt et al., 2009). (This approach contrasts with that for children with Loeys-Dietz syndrome, in which a z-score of greater than or equal to 3.5 is used as an indication for surgery.)

Summary of the literature

The natural course of aortic root dilatation in a growing child with Marfan syndrome has been described in several publications. Westaby (1999) describe how the aortic root already begins to dilate in early childhood, with a maximum increase in diameter between the ages of 6 and 14 years, followed by a decline in the pace of dilatation. In women, dilatation averaged 0.38 mm/year, and in males 0.42 mm/year (Meyboom et al., 2005). Karnebeek et al. (2001) followed 52 children and adolescents with Marfan syndrome for an average of 7.9 years. In the study group, 83% developed aortic root dilatation and 25% also showed aortic regurgitation. Eight patients underwent aortic root replacement, including two for acute dissection.

The majority of publications (Gillinov et al., 1997; Carrel et al., 2003) are from cardiac surgery groups and describe the results of aortic root surgery in relatively small numbers of children with Marfan syndrome (21 and 13 patients, respectively), without comparing outcomes with those of unoperated patients. The group of 45 Marfan patients described by Cattaneo et al. (2004) partly overlaps with the population described by Gillinov (Cattaneo

et al., 2004). The most recent study, by Everitt and colleagues, described a group of 204 children younger than 18 years, of whom 30 underwent aortic root surgery during follow-up (Everitt et al., 2009).
In the above publications, the indication for aortic root surgery was already determined in advance and primarily defined on the basis of experience (expert opinion). Indications actually differ little between the different surgical groups, effectively creating a 'common practice' (Zanotti et al., 2008).
The indication for preventive aortic root surgery in children can therefore be formulated as follows:

1) The presence of a 'giant aneurysm', which fulfills the criteria for intervention for adults, or;
2) A rapid increase in aortic root diameter (8-10 mm/year) and/or;
3) Rapidly progressive aortic regurgitation.

Based on database data from 410 patients (adults and children with and without Marfan syndrome) with aneurysms of the thoracic aorta, Davies (2006) introduced an "aortic-size index" (measured absolute aneurysm diameter in cm, divided by body surface area expressed in m^2) and defined three levels of risk for complications (rupture, dissection, death). An aortic diameter of less than 2.75 cm/mm^2 BSA equalled low risk, a diameter from 2.75 to 4.25 cm/mm^2 BSA represented a moderate risk, and an indexed aortic diameter greater than 4.25 cm/mm^2 BSA, a high risk of complications. Only 23 patients had proven Marfan syndrome and they were significantly younger, but the number of children included is not mentioned. This index does not seem to apply to young children with Marfan syndrome, in whom aortic root diameters greater than 2.75 cm/mm^2 BSA are normal.

Conclusions

Level 4	Preventive aortic root replacement is indicated in a child with Marfan syndrome if a 'giant aneurysm' is present that fulfills the criteria for intervention in adults or in the event of a rapid increase in the aortic root diameter (8-10 mm/jaar) or rapidly progressive aortic regurgitation. D Gillinov et , 1997; Carrel et al., 2003; Zanotti et al., 2008; Everitt et al., 2009

Considerations

There is only level 4 evidence for establishing the indication for aortic root replacement in a child with Marfan syndrome. This assessment is uniformly applied by several child heart surgery groups and therefore carries more weight.
Based on literature, it is not possible to indicate a z-score above which an indication for surgery in children becomes absolute.
In severely affected children with Marfan syndrome, mitral regurgitation is often prominent and this can be a reason for surgical intervention, even at a young age. Simultaneous aortic root surgery may then be considered. The risk of a second cardiac intervention is greatest when the first operation occurs at a young age and when significant mitral regurgitation is present (Gillinov et al., 1997; Everitt et al., 2009).

Valve-sparing aortic root replacement techniques require a functional and unaffected or little affected aortic valve. This may be a reason to chose aortic surgery, before aortic regurgitation arises due to a further increase in aortic root diameter.
The choice of surgical technique is determined by multiple factors. To what extent anticipated growth should role a play in this choice is unclear. In a study by Cattaneo et al. (2004), 26 children underwent a Bentall operation and during follow-up none of the survivors developed outflow obstruction as a result of the aortic prosthetic valve being too small.
Operated children with Marfan syndrome have a higher incidence of reoperation than adult patients (Gillinov et al., 1997). More than half will have to undergo reoperation within 10 years.

Recommendations

Perform preventive aortic surgery in Marfan syndrome children with a widely dilated aortic root. Criteria to be used, in addition to the Z-score, are an increase in aortic root diameter of greater than 8-10 mm/year and/or the emergence of aortic regurgitation. As evidence is lacking, the decision should be made by the responsible treatment team.

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Section 10 Clinical Follow-up

Introduction

There is no scientific literature on the need for and the frequency of medical follow-up in children or adults with Marfan syndrome.

Children

Throughout their childhood, children with Marfan syndrome are seen periodically by a variety of medical specialists, all preferably attached to and within the framework of a multidisciplinary clinic specifically designed for these children.

Frequency of assessment (see Table 10-1): these are usually determined by paediatric cardiology factors:
In case of a stable non-dilated aortic root: every 2 years.
In case of a dilated aortic root (Z < +3): every year.
In case of a dilated aortic root (Z > +3): every six months.
When determining beta blocker medication: every 3-6 months.

A paediatrician, paediatric endocrinologist or coordinating doctor sees the child at each check-up, at which a complete general physical examination takes place. In the case of extreme height increase and once a height of 150 cm has been reached, a height prediction is made by the paediatrician or paediatric endocrinologist based on bone age.
If more frequent follow-up by a paediatrician is needed than determined by the paediatric cardiologist, part of the care could be situated in a regional hospital after consultation wit the local paediatrician.

Paediatric cardiologist: sees the child at every check-up. Echocardiography at each check-up. ECG and aortic MRI, if indicated.

Paediatric orthopaedic surgeon: sees the child by indication, based on musculoskeletal complaints or at the instigation of the paediatrician/coordinator.

Geneticist: sees the child at the time of diagnosis, for the results of DNA diagnostics and then by indication.

Table 10.1 Follow-up scheme for children with Marfan syndrome

Specialist	Type of follow-up	Frequency
paediatric cardiologist	echocardiography, ECG	Stable non-dilated aortic root every 2 years; dilated aortic root but Z <+3 every year; dilated aortic root Z >+3 every 6 months
coordinating doctor[1]	physical examination; height prediction (at 150 cm or in case of extreme height increase); signalling of psychosocial problems; coordination of care	every assessment based on the cardiologic factors[2]
paediatric ophthalmologist	refraction test, slit lamp examination in maximum mydriasis	no important ophthalmologic abnormalities every 2 years; in case of ophthalmologic abnormalities, depending on the findings
paediatric orthopaedic surgeon	physical examination, X-ray	if indicated
clinical geneticist	at diagnosis, for results DNA-analysis	if indicated

[1] this can be a paediatrician or clinical geneticist
[2] if more frequent follow-up by a paediatrician is needed, part of the care could be situated in a regional hospital after consultation wit the local paediatrician

Paediatric ophthalmologist: sees the child at first examination, then if no important ophthalmological abnormalities, every two years. In the case of significant abnormalities (usually lens (sub)luxation), frequency of inspection dependent on eye abnormalities. If the initial examination takes place during the first year of life, then repeat within one year.

Surveillance after cardiac surgery: in children, ultrasound examination is generally sufficient.

Adults

Life-long and regular clinical assessment is carried out in a Marfan center, with the involvement of specialists with extensive expertise in this area. Annual check-ups by a cardiologist are usually sufficient. In patients who have undergone surgery of the thoracic aorta, it is important that the cardiologist and cardio-thoracic surgeon agree on which of them will continue to monitor the patient on specific issues related to the aorta. Referral to other specialties occurs as indicated, and specific examinations will be dictated by symptoms.

Ophthalmologist:
There are indications that primary open-angle glaucoma is more common in patients with Marfan syndrome (Izquierdo et al, 1992; Nahum & Spierer 2008). Therefore, periodic examination of eye pressure and the aspect of the optic nerve should be considered. In most cases, an ophthalmologist local to the patient may become involved.

Echocardiography:
In stable patients, an annual outpatient check-up involving echocardiography of the aortic root is recommended. Valve regurgitation and ventricular function can also be effectively monitored using echocardiography.

MRI:
Baseline MRI imaging of the entire aorta is performed at first check-up and repeated at least every 5 years as long as the dimensions beyond the aortic root are normal. In cases of aneurysm formation in the distal aorta, a repeat MRI is indicated at least annually. CT scintigraphy can replace MRI if there is a contraindication for MRI, such as claustrophobia or a pacemaker, and CT can sometimes be more suitable than MRI for the early detection of complications following aortic surgery. See Considerations in the section Imaging.
A patient should be assessed annually by CT (or MRI) in the event of a chronic aortic dissection, in order to allow timely detection of aneurysm formation (Hiratzka et al., 2010). The elasticity of the aorta can also be measured with MRI, and elasticity of the thoracic descending aorta may have predictive value for the occurrence of progressive local growth (Nollen et al., 2004).

If there is an indication for elective surgery, the probability of coronary artery disease can be assessed using a CT scan, as catheter interventions entail a certain risk in patients with a dilated and weakened aortic wall. If the CT scan shows indications for coronary artery disease, the catheterisation will, however, still be required.

For optimal comparison, repeated measurements of the aortic diameter should be performed using the same technique.

Follow-up after aortic surgery:
In adults, a baseline CT/MRI should be made prior to discharge and repeated after 6 months, 1 , 2 and 3 years. In case of stable diameters, a frequency of once every 2 years is sufficient, but surveillance should be increased as soon as growth is observed.

Recommendations

Children
Follow-up of children with Marfan syndrome should take place within a multidisciplinary Marfan clinic team.

If more frequent paediatric follow-up is needed than the cardiologic follow-up, part of the paediatric care can be performed by a regional paedriatrician after consultation.

Ophthalmologic follow-up should take place at least every two years.

Ultrasound follow-up of the aorta after cardiac surgery is generally sufficient.

Adults
Adult Marfan patients should receive life-long check-ups, provided by a cardiologist attached to a Marfan clinic or alternately by a cardiologist attached to a Marfan clinic and a regional cardiologist.

Assessments by an ophthalmologist or orthopaedic surgeon take place as indicated.

Consider periodic follow-up for eye pressure and the optic nerve.

Folowing aortic surgery, perform a baseline CT/MRI before discharge. Repeat after 6 months, 1, 2, 3 years and then every 2 years. Intensify surveillance as soon as growth is observed.

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Section 11 Family Studies

Introduction

Due to the dominant mode of inheritance, family studies are important in Marfan syndrome, and the intra-familial variability of the disorder means that it is not always clear which family members may or may not be affected. Family studies in Marfan syndrome are no different to those in other inherited disorders, especially if the mutation in the FBN1 gene is known. The question is how studies will be conducted, in which family members, and where the research will take place.

Summary of the literature

Using the original 'Ghent criteria' (De Paepe A. et al, 1996), 91% of individuals conforming to a diagnosis of Marfan syndrome showed an *FBN1* mutation, which confirmed the diagnosis at the genetic level (Loeys et al, 2004). In a recent publication by Sheikhzadeh, an *FBN1* mutation was detected in 80% of the patients who met the original, the new, or both Ghent criteria (Sheikhzadeh et al, 2011). There is no specific literature that focuses on methodologies for family studies in Marfan syndrome.

Conclusions

Level 3	A mutation in the FBN1 gene can be demonstrated in most patients with Marfan syndrome. C Loeys et al, 2004; Sheikhzadeh et al, 2011

Considerations

When a pathogenic mutation in the *FBN1* gene is detected in an index patient, use is made of the 'cascade-screening' customary in clinical genetics. This involves the examination of (vertical) first-degree relatives in first instance, followed by wider screening depending on the position of the family members that tested positive. Brothers and sisters of the affected person will be examined if a parent has Marfan

syndrome or if anamnestic evidence points to Marfan syndrome in the siblings. Prior to blood withdrawal, the implications of possible DNA test results should be explained and discussed with family members by a clinical geneticist or genetic counsellor, especially where relatives are apparently healthy (presymptomatic DNA diagnostics). Depending on the time required for a DNA diagnostic test, in the case of a new index patient, and where appropriate, one can consider echocardiography in first-degree relatives of the index patient if there is strong suspicion of Marfan syndrome in a family member or high levels of anxiety.

If no pathogenic mutation of *FBN1* is found in the index patient, a diagnostic examination is conducted as described in the section Diagnostics. This includes physical, cardiological and ophthalmological examination in all cases.

In practice, it is strongly recommended that the relatives of a Marfan syndrome patient be referred to a specialised Dutch Marfan clinic for diagnostics (where a clinical geneticist is involved).

Recommendations

Perform DNA analysis in the relatives of Marfan patients where possible, and otherwise by clinical diagnosis. Apply so called 'cascade screening': vertical (at risk) first-degree relatives are the first to be screened.

DNA diagnostics in relatives must take place in a clinical genetic centre, and clinical diagnosis - where appropriate - in a multidisciplinary Marfan clinic.

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Section 12 Pregnancy and Delivery

Introduction

Literature and hard data related to pregnancy, childbirth and Marfan syndrome are relatively scarce. The questions central to this section are: "What are the risks of pregnancy and childbirth for mother and child?", and "What are the recommendations for the guidance of pregnancy and childbirth?".
Large randomised trials are lacking, as most literature consists of case reports. This leaves considerable room for expert opinion in the treatment recommendations for pregnant women with Marfan syndrome. Progress has been made in treatment and there is now a better understanding of the genetics and natural history. In this regard, studies of the effects of beta-blockers during pregnancy are promising but have yet to be completed.
Multidisciplinary teamwork and a clear treatment plan, are important in pregnant women with Marfan syndrome.
The section is divided into two subsections. The first subsection concerns the risks of pregnancy and childbirth for mother and child. The second subsection concerns the supervision of pregnancy and childbirth. At the end a checklist is included.

1. Risks of pregnancy and delivery for mother and child

Summary of the literature
Most literature consisted of case reports, with only a few of reviews and studies in patient groups.
The main complications for pregnant women with Marfan syndrome are cardiovascular events, aortic dissections in particular. The physiological changes during pregnancy (increased cardiac output (30-50%) and increased blood volume) constitute an extra burden on the heart and major blood vessels. Cardiac output increases by a further 20% during the contractions of labour, and an extra burden is also present immediately after delivery (Hytten & Paitin, 1963; Wallenburg, 1990; Silversides et al., 2010). In addition, the hormonal changes during pregnancy have a negative influence on the strength of the aortic wall (Manola-Estrella & Barker, 1967).

1.1 Aortic dissections

The incidence of aortic dissection in the general population is about 2.9-3.5/100,000

person-years (Ramanath et al, 2009). The risk in pregnant Marfan patients is estimated to be 1-5% (Pacini et al., 2009; Lind & Wallburg, 2001; Canadas, 2010). This seems to be related to aortic diameter, aortic diameter growth, family history and previous surgery on the aorta. (Preconceptional) counselling is therefore an important component of care for pregnant women with Marfan syndrome.

The likelihood of an aortic dissection during pregnancy

The average age at which a dissection occurs in Marfan patients is around 30-32 years (Murdoch et al., 1972; Silverman, 1995). A dissection can occur in any trimester in pregnant women, but the greatest risk is in the last trimester and in the postpartum period. From two cases series including 57 (Husebeye et al., 1958) and 51 patients (Konishi et al., 1980) and a literature review by Lind (2000), it appears that around 5% of dissections occur in the first trimester, 10% in the second trimester, 50% in the third trimester, 15% during delivery and 20% in the postpartum period. Only a relatively small number of dissections have been described in the literature (500-600).

Meijboom (2005) followed changes in aortic diameter for an average of 6.4 years in a group of 127 female Marfan patients. Within this group, changes in aortic root diameter could be followed in 31 (22 females) pregnancies, and were compared with 22 matched patients who did not become pregnant during the follow-up period. In the pregnant group, no significant change was found in the aortic root diameter prior to, during and following pregnancy. There were also no significant differences in diameters between women who were or were not pregnant. However, within the 'pregnant' group a significant difference was seen in increases in aortic root diameter in those women with an initial aortic root diameter ≥40 mm, compared to women with a diameter <40 mm. There was also a significant difference in the long-term increase in aortic root diameter of 'pregnant' women with an initial aortic root diameter ≥40 mm and matched controls. In the group of pregnant women with an aortic root diameter of 40-45 mm and no haemodynamic abnormalities (n = 9; 11 pregnancies), no aortic dissections or aorta-related complications were found.

An aortic root diameter <40 mm is considered a relatively safe limit for women with Marfan syndrome who wish to become pregnant.

The European guideline (Regitz-Zagrosek et al., 2011)) also adheres to a limit of 40 mm. Furthermore, the guideline states:

a. An aortic root diameter of >40 mm and an increase in diameter of the aortic root during pregnancy are risk factors for dissection in pregnant women with Marfan syndrome;

b. Pregnancy is not recommended at aortic root diameters greater than 45 mm;
c. During the counselling of women with Marfan syndrome with an aortic root diameter of 40-45 mm, risk factors such as aortic growth and family history of dissection should be taken into account.

The Canadian guideline (Silversides et al., 2010) extends the threshold above which a pregnancy is not recommended to 44 mm.
Almost all literature indicates that even when the aortic root diameter is <40 mm, there is no guarantee that a dissection will not occur.

Pregnancy is discouraged in patients who have experienced a type A or B dissection (Regitz-Zagrosek et al, 2011).

Possibilities for prevention of aortic dissection
Beta blockers could potentially reduce the risk of aortic dilatation (Regitz-Zagrosek et al, 2011). It is recommended that prophylactic treatment with beta blockers be either continued or initiated, regardless of aortic diameter or length of pregnancy (Regitz-Zagrosek et al, 2011; Goland et al., 2009; Canadas, 2010; Pacini et al., 2009). Beta-blockers have been linked to foetal growth retardation and neonatal bradycardia, hypoglycemia, hyperbilirubinemia and apnea but these complications are generally rare. The maternal clinical benefits far outweigh these risks (Magee & Dukey, 2003).
In practice, metoprolol is most widely prescribed; atenolol has been more frequently linked to foetal growth retardation (Hogstedt et al., 1985).
The detection and treatment of high blood pressure is important. Beta blockers are not indicated for the treatment of gestational hypertension, with the exception of labetolol, which has postsynaptic α_1- en non-selective β-sympatholytic properties (NVOG 2005). Other agents which may be used for the treatment of gestational hypertension/pre-eclampsia include nifedipine, nicardipine and aldomet.
ACE-inhibitors and AT1-receptor blockers are contraindicated in pregnancy due to teratogenic effects (Cooper et al., 2006; Alwan et al., 2005).

In cases of planned pregnancy, both the ESC guideline 2011 and the Canadian guideline advise preconceptional preventive surgery at aortic root diameters above 45 mm (leading edge to leading edge).

Treatment of aortic dissection during pregnancy

Most acute situations involve a type A dissection (ascending aorta), and immediate surgery is required.

The length of gestation is of importance when considering whether a pregnancy should be terminated in cases of a type A dissection. At a gestational age of more than 30 weeks, a caesarean section is usually carried out and immediately followed by surgery of the aorta. The period between 24-30 weeks is still under debate. An emergency caesarean followed by surgery is common practice but in cases of extreme prematurity, one can elect to continue the pregnancy and to perform the operation under foetal monitoring, and with adjustments in anaesthesia and hypothermia. The risk of severe neonatal morbidity is about 3-6% and foetal mortality is high (Chambers, 1994). When a dissection occurs at a gestational age of less than 24 weeks, the same dilemmas have to be faced.

Type B dissections (no involvement of ascending aorta) are generally treated by conservative drug treatment with frequent monitoring by MRI. Surgery may be indicated in symptomatic dilatation of the descending aorta. If a foetus is viable, the European guideline recommends a caesarean section first, immediately followed by treatment of the aorta (Regitz-Zagrosek et al, 2011).

1.2 Other complications of pregnancy and delivery

The rate of spontaneous abortion in women with Marfan syndrome may be slightly increased (15-20%; normal 10-15%) (Meijboom et al., 2006; Lind, 2000; Lind et al., 2001; Rossiter et al., 1995) .

Premature birth and dysmaturity are also somewhat more frequent (5-30% and 10-15%, respectively, normally about 8% and 10%) (Lind et al., 2001; Rossiter et al., 1995; Lipscomb et al., 1997).

Little information is available on the incidence of postpartum bleeding, manual placental removal and total rupture in Marfan syndrome compared with the normal population, but it does not seem to greatly deviate from that of the normal population (Lind, 2000; Lind et al., 2001).

Published data specifically focused on pregnant women with Marfan syndrome and scoliosis is lacking. The percentage of caesarean sections in non-Marfan patients with scoliosis is no higher than in the normal population(Betz et al., 1987; Orvomaa et al., 1997).

Neonatal outcome is correlated with maternal health. If no cardiac or vascular surgery/ complications occur during pregnancy, neonatal outcome is comparable to that of a normal population (Regitz-Zagrosek et al, 2011).

Conclusions

Level 2	Aortic dissection is a major complication of pregnancy in women with Marfan syndrome, and occurs in 1-5% of cases. B Lind et al., 2001; Pacini et al., 2009 D Canadas, 2010
Level 3	Most aortic dissections occur in the 3rd trimester, during delivery and postpartum. C Husebeye et al., 1958; Konishi et al., 1980
Level 3	The probability of an aortic dissection during pregnancy is small, where the aortic diameter is stable and less than 40-45 mm. B Meijboom et al., 2005
Level 4	A type A dissection is an indication for emergency surgery. A type B dissection is usually treated conservatively. Depending on the findings and symptoms, a type B dissection may be treated surgically or by placing a stent. D Regitz-Zagrosek et al, 2011
Level 4	A type A dissection is an indication for emergency surgery. A type B dissection is usually treated conservatively. Depending on the findings and symptoms, a type B dissection may be treated surgically or by placing a stent. D European Society of Cardiology 2011

Level 4	The risk of spontaneous abortion or preterm birth in women with Marfan syndrome may be slightly elevated. C Meijboom et al., 2006; Lind et al., 2001; Rossiter et al., 1995; Lipscomb et al., 1997

Considerations

The probability of an aortic dissection in pregnancy is lower with elective aortic surgery in the anamnesis than with a history of surgery for acute aortic dissection. Although no studies or literature are known, it is generally believed that the risk of dissection in pregnancy following elective aorta surgery is acceptable. In cases with a history of surgery for acute aortic dissection, the aorta is known to be poor and to carry an increased risk of a new dissection. In this case, a pregnancy is discouraged.

Recommendations

Do not discourage women with Marfan syndrome and an aortic root diameter of less than 40 mm from becoming pregnant.

When making decisions on pregnancy, in cases of aortic root diameters of 40-45 mm, individual risk factors should be taken into account.

Encourage patients with an aortic root >45 mm to undergo elective aortic root replacement before becoming pregnant.

Advise against pregnancy in patients who have experienced an aortic dissection.

Diagnose high blood pressure actively and treat it.

Continue or begin prophylactic treatment with beta blockers during pregnancy.

2. Guidance during pregnancy and delivery

Summary of the literature

2.1 Pregnancy

There is little to no scientific literature on pregnancy guidance in Marfan patients. The recommendations therefore predominantly reflect the opinion of the working group.

2.2 Anticoagulants during pregnancy

Anticoagulants are indicated for a proportion of female Marfan patients, due to valve defects or following cardiovascular surgery.

There is no evidence that the use of anticoagulants in a pregnant patient with Marfan syndrome entails specific increased risks, but oral anticoagulants do cause an increased risk of miscarriage and haemorrhagic complications in pregnant women (Schaefer, 2006).

Patients taking anticoagulants should receive counselling appropriate to their situation. Congenital anomalies have been described following the use of coumarin derivatives, but not following the use of heparin and low molecular weight heparin (LMWH) derivatives (these substances do not cross the placenta). If oral anticoagulants (Marcoumar/ Sintromitis) were already in use before pregnancy, it is preferable to use Heparin/LMWH in the first and at the end of the 3^{e} trimester, and to prescribe coumarin derivatives in the intervening period. In general, a daily dose of <2 mg Sintromitis dfoes not result in teratogenic effects and can therefore be considered for use throughout pregnancy. The use of LMWH throughout pregnancy has been linked to a slightly increased risk of thrombosis in patients with non-biological prosthetic valves (Yinon, 2009). Concentrations of LMWH may fluctuate during pregnancy, potentially resulting in a fall of anti-Xa-activity below the therapeutic value (Friedreich, 2010; Barbour, 2004).

Prolonged use of unfractioned heparin can result in complications such as osteoporosis and “heparin-induced thrombocytopenia”. The use of ascal is acceptable, if indicated (NICE 2010).

2.2 Delivery

No scientific studies were found in which the risk of vaginal birth was compared with caesarean sections in women with Marfan syndrome. Reviews and guidelines do provide recommendations, but they are mainly based on expert opinion.

The European Society of Cardiology (Regitz-Zagrosek et al, 2011) provides recommendations and advice on parturition, based on the WHO risk classification. See Tables 12.1, 12.2 and 12.3.

Table 12.1 Modified WHO classification of maternal cardiovascular risk: principles

Risk class	Pregnancy-related risk with this condition
I	No detectable increased risk of maternal mortality and no/mild increase in morbidity.
II	Small increased risk of maternal mortality or moderate increase in morbidity.
III	Significantly increased risk of maternal mortality or severe morbidity. Expert counselling is required. If pregnancy is decided upon, intensive specialist cardiac and obstetric monitoring is needed throughout pregnancy, childbirth and puerperium.
IV	Extremely high risk of maternal mortality or severe morbidity: pregnancy is contraindicated. If pregnancy occurs, termination should be discussed. If pregnancy continues, care as for class III.

Table 12.2: Risk classification of the various cardiovascular abnormalities that may occur in Marfan syndrome

Risk class	Condition
WHO II-III	Mild left ventricular dysfunction. Marfan syndrome without aortic dilatation.
WHO III	Mechanical valve. Marfan syndrome and aorta between 40-45 mm.
WHO IV	Marfan syndrome and aorta >45 mm.

Table 12.3 : Recommendations based on risk classification

Recommendation	Level of recommendation[a]	Level of proof[b]
Marfan and aorta >45 mm: surgery before pregnancy	I	C
Ascending aorta <40 mm: vaginal delivery is favoured	I	C
In cases of severe hypertension: vaginal delivery with epidural and possibly elective assisted delivery	IIa	C
Marfan and aorta between 40-45 mm: vaginal delivery with epidural anaesthesia and expedited second stage should be considered	IIa	C
Marfan and aorta between 40-45 mm: caesarean delivery may be considered	IIb	C
Aorta >45 mm and Marfan syndrome: caesarean delivery should be considered	I	C
Type B dissection or history of type B dissection: should be advised against pregnancy*	III*	C
If delivery starts while on oral anticoagulants, caesarean delivery is indicated	I	C

Two non-systematic reviews have suggested that women at low risk can undergo vaginal birth, provided there are no obstetric or other contraindications (Canadas, 2010(II), Goland et al., 2009).
Both Goland et al. (2009) and Canadas et al. (2010) recommend the liberal use of epidural anaesthesia and forceps or vacuum pump during vaginal delivery, in order to reduce effects on blood pressure and to accelerate the second stage of labour.
A position on the left side or half sitting places the least stress on the aorta during labour (Regitz-Zagrosek et al, 2011).

In cases with a high risk, a controlled setting is usually chosen and a primary caesarean section performed, together with intensive maternal monitoring and, if possible, fractionated administered epidural anaesthesia with haemodynamic monitoring (Canadas, 2010; Goland et al., 2009).

The ability to administer epidural or spinal anaesthesia can sometimes be limited by dural ectasia (Goland et al., 2009; Canadas, 2010), previous back surgery, scoliosis or prolonged bleeding (anticoagulants). Dural ectasia cause the spinal block to fail through the dilution of the local anaesthetic agent and are responsible for a higher chance of a “dural tap” at the epidural punction.

A caesarean section is recommended in patients who enter labour while using oral anticoagulants (OAC), to prevent intracranial haemorrhage in the foetus. The OAC can cross the placenta and affect coagulation in the foetus (Regitz-Zagrosek et al, 2011).

Conclusions

Level 3	As a consequence of fluctuating concentrations of LMWH, anti-Xa activity may fall below the therapeutic concentration and should be monitored. C Friedreich, 2010; Barbour, 2004

Level 4	Vaginal delivery is safe in patients at low risk (aortic diameter <40 mm and no haemodynamic abnormalities). According to the ESC guideline, both vaginal and caesarean delivery should be considered in cases with a moderately increased risk, depending on individual circumstances. High risk cases (aortic diameter >45 mm, history of acute aortic dissection, haemodynamic limitations) usually undergo a primary caesarean section performed with intensive maternal monitoring and, if possible, fractionated administered epidural anaesthesia with haemodynamic monitoring. D Canadas, 2010 II; Goland et al., 2009; Regitz-Zagrosek et al, 2011

Level 4	The advice in literature is for liberal use of epidural anaesthesia and forceps or vacuum pump during vaginal delivery, in order to reduce the cardiovascular burden during the second stage of labour. D Goland et al., 2009; Canadas, 2010

Considerations

A preconceptional consultation is important and should include: a gynaecologist, a clinical geneticist, a cardiologist and a paediatrician. During this consultation, the dangers, the strategy and plan of treatment can be determined in advance and discussed. An anaesthesiologist can be consulted preconceptionally, but should always be consulted before delivery.
If no preconceptional consultation has taken place, the above consultation should take place as early as possible in pregnancy and a written treatment plan should still be prepared. The antenatal check-ups can, in principle, take place at regular intervals as described in the NVOG protocols. On theoretical grounds, frequent monitoring from 28 weeks appears logical.

Besides the routine 1e trimester foetal ultrasound (period; 11-14 weeks scan), a so-called advanced ultrasound examination of the foetus around 20 weeks gestation may be considered, with a repetition at 30-34 weeks. Although the chance of a foetus being

affected by congenital abnormalities visible on ultrasound is very small, there are case reports and personal communications that report large aortic diameters antenatally. Moreover, it is undesirable to overlook a foetal abnormality in a pregnancy that is already hazardous.

Periodic monitoring of aortic dimensions is clearly required. In the literature, no clear indications are given for the frequency of monitoring, but a general scheme is: before pregnancy, at 20-24 weeks, 36 weeks, 2 days postpartum and 6 weeks postpartum. Depending on the history and clinical findings, more frequent monitoring may possibly be indicated. In high-risk patients, the abdominal aorta should also be properly examined.

The choice of the mode of delivery depends not only on the risk, but also on individual circumstances and patient preference. The patient should be well-informed about the risks of the various options.
The safety of the mother and the child should take priority when making any choice.
Parturition should take place at the secondary or tertiary level, depending on the cardiovascular status of the patient and treatment capabilities of the hospital.
Low-risk patients (aortic diameter <40 mm) can receive check-ups and undergo childbirth at the secondary level, as long as clear agreement is reached with a cardiosurgical centre on check-ups, treatment and measures around parturition, and that the circumstances requiring referral are clearly discussed. A treatment plan for possible emergencies is important. Patients with moderate or high risk must give birth in a tertiary center with capabilities in cardiovascular surgery and an experienced team should be present.

Depending on general health and the results of cardiological investigations, in a medium-risk situation (aortic diameter 40-45 mm or 1x elective aortic surgery or heart valve replacement with a stable haemodynamic result) it is possible to opt for a vaginal delivery with progressive epidural anaesthesia, basal maternal monitoring and possibly a primary assisted vaginal delivery (forceps/vacuum extraction).

If medication is used by a mother during pregnancy, a consultation with a paediatrician is indicated following childbirth.

Recommendations

Both a (multidisciplinary) preconceptional consultation and a multidisciplinary treatment plan are important in Marfan patients planning pregnancy.

Consider a so-called advanced ultrasound examination of the foetus, in addition to routine foetal ultrasound, at around 20 weeks and around 30-34 weeks of pregnancy.

Pregnant Marfan patients should receive check-ups at the secondary or tertiary level, and these should include periodic monitoring of aortic diameter (before pregnancy, at 20-24 weeks, 36 weeks, 2 days postpartum and 6 weeks postpartum). Depending on history and clinical findings, more frequent monitoring may possibly be indicated and monitoring of high-risk patients should also include the entire abdominal aorta.

Patients on anticoagulants should receive appropriate counselling. Check coagulation using the indicator of anti-Xa activity during therapeutic use of LMWH. If delivery occurs while oral anticoagulants are still being used, a caesarean section is indicated.

Advise a vaginal birth in a secondary centre for patients at low risk (aortic diameter < 40 mm and no haemodynamic abnormalities), provided that arrangements with a tertiary centre are made in case of problems or complications. Use epidural anaesthesia and forceps or vacuum pump liberally, in order to reduce effects on blood pressure and to accelerate the second stage of labour.

Consider a primary progressive epidural and primary assisted delivery (vacuum/forceps extraction) at parturition, with fractionated administered epidural anesthesia and haemodynamic monitoring in patients at moderate risk (aortic diameter 40-45 mm or 1x elective aortic surgery or heart valve replacement with a stable haemodynamic result). Consider a caesarean section depending on individual circumstances.

Perform elective caesarean section with intensive maternal monitoring and with fractionated administered epidural anaesthesia and haemodynamic monitoring, if possible, in high-risk cases (aortic diameter >45 mm or acute aortic dissection or haemodynamic limitations) in the presence of an experienced team.

Patients at moderate or high risk should give birth in a tertiary care centre with options for cardiovascular surgery

The choice of the mode of delivery should be made in consultation with the patient.

If medication is used during pregnancy, a consultation with a paediatrician is indicated following childbirth.

Checklist: pregnancy and Marfan syndrome

Preconceptional consultation:

- Cardiovascular evaluation;
- Adjustments to medication: anticoagulants, ACE inhibitors, beta-blockers;
- R/ folic acid;
- Consultation with cardiologist and possibly other specialists as needed;
- Pregnancy preferably at a younger age;
- Prenatal diagnosis, consultation with clinical geneticist;
- General physical examination;
- Explanations of chance of aortic dissection, prevention, treatment, complications;
- Possible adjustments to lifestyle;
- Pregnancy check-ups at secondary/tertiary level, depending on health.

Pregnancy:

- Cardiovascular evaluation;
- Explanations of chance of aortic dissection, prevention, treatment, complications;
- Monitoring of aorta (at 20-24 and 36 weeks);
- Possible lifestyle guidelines;
- Consultation with cardiologist, anaesthesiologist and possibly other specialistss as needed;
- Consultation at a cardiosurgical centre;
- Prenatal diagnosis;
- Ultrasound: 11-13 weeks scan, 20 weeks ultrasound/advanced ultrasound examination type 1, 30-34 weeks scan, growth monitoring;
- Prepare a birth plan;
- Consultation with a paediatrician;
- Medication (anticoagulants, beta blockers, etc.);
- General physical examination;
- From approximately 28 weeks, more frequent check-ups in order to monitor blood pressure.

Childbirth:

- If risk is low and aortic diameter <40 mm: secondary/tertiary level, vaginal delivery;
- If risk is moderately increased (decided at multidisciplinary consultation): vaginal delivery, tertiary level, maternal monitoring, epidural anaesthesia and primary

assisted vaginal delivery or caesarean section;
- If high risk: tertiary level, intensive maternal monitoring, epidural anaesthesia, a primary caesarean section if possible.

Postpartum:
- Contraception;
- Evaluation of neonate;
- Ultrasound of aorta (2 days and 6 weeks postpartum).

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Section 13 Prenatal and Preimplantation Diagnosis

Introduction

Many patients with Marfan syndrome reach reproductive age in good health, thanks to the effective treatment options. Patients often have questions concerning fertility, pregnancy-related complications and the consequences for the child. Since Marfan syndrome is an autosomal dominant disorder, the chance that a Marfan parent will have a child with Marfan syndrome is 50%. As a molecular cause is currently found in a large percentage of Marfan patients, opportunities are available for prenatal diagnosis (PND) or preimplantation genetic diagnosis (PGD).

Brief explanation of procedure prenatal/preimplantation genetic diagnosis
Prenatal diagnosis of an existing pregnancy allows foetal material to be examined for a specific condition by chorionic villus sampling or amniocentesis. Chorionic villus sampling takes place via either the abdomen or vagina, around the 11th week of pregnancy. Amniocentesis can be performed from the 16th week onwards. PND involves certain risks: in general, the risk of miscarriage as a result of a chorionic villus sampling/amniocentesis is approximately 0.3-0.4%.

Preimplantation genetic diagnosis involves an IVF procedure whereby genetic diagnosis takes place prior to transfer of the embryo, and only embryos lacking a mutation will be returned. If a couple chooses PGD, the laboratory must conduct preliminary genetic research of the parents themselves, any children and any relatives. The duration of the preliminary investigation can vary from several weeks to one year. Since the *FBN1* gene is not prone to hot spot mutations and each family carries a specific mutation, marker analysis is usually chosen (Spits et al., 2006; Kilpatrick et al., 1996).

A gynaecologist, a clinical geneticist and a social worker will discuss the course of these studies (preparation, sampling, results, psychosocial aspects) with the prospective parents.

Summary of the literature
A literature search was carried out with the aim of identifying whether PND and PGD carry specific risks in the context of Marfan syndrome. If the father has Marfan syndrome, PND/PGD is not expected to entail a higher risk than for any other indication for PND/PGD, as the expectant mother is healthy. However, in the event that the woman herself has

Marfan syndrome and wishes to become pregnant, there are theoretical additional risks to consider, including those of the tests (chorionic villus sampling/amniocentesis/follicular puncture), the hormonal stimulation in PGD, the multiple pregnancy risk with PGD and the use of anticoagulants.
The specific cardiac-related risks for a woman with Marfan syndrome during pregnancy are discussed in section 12.

The literature related to prenatal/preimplantation genetic diagnosis and Marfan syndrome is limited to individual case reports (Blaszczyk et al., 1998, Godfrey et al., 1993; Harton et al., 1996, Kilpatrick et al., 1996, Smith et al., 2010) and a few small series (Loeys et al., 2002; Toudjarska et al., 2001; Spits et al., 2006). These articles report that prenatal/preimplantation diagnosis is possible, but do not discuss possible risks.

Whether amniocentesis/chorionic villus sampling/follicular puncture in an expectant mother with Marfan syndrome carries a higher risk of abortion than in the general population has not been studied. No complications associated with these procedures were found in the literature.

Adverse effects in female Marfan patients due to ovarian stimulation during an IVF procedure have not been described in the literature.

No report of a multiple pregnancy entailing additional risks for a Marfan patient could be found in the literature. The PGD guideline for Marfan syndrome includes no comment on the number of embryos that should be transferred. In general, the cardiac condition of a patient is taken into account (even for indications other than Marfan syndrome), and in consultation with the clinical geneticist, cardiologist and gynaecologist, 1 or 2 embryos will be transferred.

If a biopsy is to be performed on a woman using anticoagulant medication, this should be discussed with the cardiologist. Complications resulting from the use of anticoagulants in a pregnant patient with Marfan syndrome have not been described.

Conclusions

Level 3	Prenatal diagnosis for pregnancies that carry an increased risk of Marfan syndrome is possible if the familial mutation is known (or if there is linkage). A choice can be made between chorionic villus sampling (10-12 weeks gestation) or amniocentesis (15 - 18 weeks gestation). C Loeys et al, 2002; Toudjarska et al, 2001; Spits et al, 2006
Level 3	Pre-implantation genetic diagnosis for pregnancies that carry an increased risk of Marfan syndrome is possible if the familial mutation is known. C Loeys et al, 2002; Toudjarska et al, 2001
Level	No information is available from literature on whether invasive diagnosis (chorionic villus sampling/amniocentesis/follicular puncture) entails greater risks in a couple with Marfan syndrome than in the general population. No literature
Level	It is not known whether IVF-related hormone stimulation leads to increased risks for Marfan patients. No literature

Considerations

There is no scientific literature to support the conclusion that PND or IVF for PGD is contraindicated for Marfan female patients. Conversely, it can also not be concluded that there is no additional risk. On the basis of small series and personal experience, PND and PGD does not seem to present a major risk to pregnant Marfan patients.

The clinical variability of Marfan syndrome leads to complex reproductive choices, since a molecular diagnosis does not predict the severity of symptoms.
Theoretically, a twin pregnancy is less desirable because of the additional cardiovascular

stress. This is particularly important in cases where ovulation induction or IVF (with or without pre-implantation diagnosis) is applied, with the related increased risk of multiple births.

Recommendations

Prenatal or preimplantation genetic diagnosis is possible when the familial mutation of a parent with Marfan syndrome is known.

Offer (or re-offer) genetic counselling to young adults (male or female) with Marfan syndrome. Recurrence risk, cardiac condition before and during pregnancy and reproductive options should be discussed during this preconception counselling.

Do not transfer more than a single embryo during IVF.

The risks of PND and PGD for IVF should be studied in larger series

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Section 14 Lifestyle Recommendations

Introduction

The international guidelines on Marfan syndrome (Maron et al, 2004; Pelliccia et al, 2005; Maron et al, 2005a) advise patients to change their lifestyle. These recommendations mainly concern sport; advice related to daily activities and career choice is more limited. The motivation for lifestyle advice is to reduce the haemodynamic stress on the aortic wall. The increases in heart rate, blood pressure and stroke volume during intense activity may promote the development of aortic aneurysms and increase the rate of aortic dilatation. Distensibility declines and wall stress increases during progressive aortic dilatation, resulting in an aortic wall that is even less capable of compensating for the effects of haemodynamic stress during exercise and is thus at greater risk of aortic dissection or rupture (Elefteriades, 2008). Besides physical exertion, strong emotions also seem to play a role in the occurrence of aortic dissection (Hatzaras et al, 2007).

Limiting normal sports activity in children and adolescents with Marfan syndrome can have a dramatic effect, and may well have a negative impact on the physical and psychosocial well-being of the child. Adult Marfan patients experience this obligatory adjustment of their activity pattern as negative for their quality of life (Peters et al, 2001).

Summary of the literature

A *scientific statement* from the American Heart Association in 2004 (Maron et al, 2004) included advice on physical activity and **recreational** sport for young people with genetic heart disease, including Marfan syndrome. These recommendations were based primarily on the experience and insights of the panellists (expert opinion). Quote: "*There is a paucity of precise published evidence. Indeed, the panel encountered few absolute and truly quantitive data...*". When formulating their advice, the panellists attempted to strike a balance between the positive effects of sports activity and the inherent risks for this particular patient group.

Avoiding participation in sports that involve rapid accelerations and decelerations (e.g. basketball, squash and tennis) and those that demand intensive isometric (= static) exertion is advisable for all individuals with Marfan syndrome.

School gym classes deserve particular attention. Activities during school gym and outdoor play are acceptable at all times for junior school children, but competitive sports tests in high school are not suitable. The above recommendations are not applicable to Marfan patients who have already had surgery, as more stringent recommendations generally apply to this group.
In 2005, the European Society of Cardiology (ESC) published recommendations for participation in **competitive** sports, also at the level of expert opinion (Pelliccia et al, 2005). Competitive sport is not recommended for Marfan patients, at any age. Low intensity, recreational sport is acceptable. Contact sports are not recommended because of the risk of damage to the aorta or eyes. Moderately intense, **recreational** sports are allowed in individuals with normal aortic root dimensions. Recommendations have also been formulated for individuals with clinically suspected Marfan syndrome, but without definite genetic confirmation.

Aortic root diameter is at the centre of the recommendations formulated in 2005 at the 36th Bethesda Conference (BC#36) of the American College of Cardiology (ACC). Participation in low and moderate intensity static and low dynamic competitive sports is allowed if the aortic root diameter is below 40 mm or below 2SD in children, in the absence of haemodynamically significant mitral regurgitation and a family history of aortic dissection or sudden death. It is advisable to measure aortic root diameter by echocardiography every six months.
Marfan patients with an aortic root diameter above 40 mm or above 2SD in children with previous aortic surgery, chronic aortic dissection, moderate to severe mitral regurgitation and/or a family history of dissection or sudden cardiac death, may only participate in low intensity competitive sports. Participation in contact sports is not recommended for anyone with aortic dilatation, and in particular, for patients taking anticoagulant medication (Maron and Zipes, 2005b).
There are several published lists that provide a classification of the intensity of exercise in sports. The scheme by Mitchell et al (2005) may be helpful but the advice regarding sports is largely dependent on the individual situation of the patient (Mitchell et al, 2005).

In 2008, Pelliccia et al. (2008) compared the advice of the ESC and that of the ACC: the differences centred on whether or not to allow participation in competitive sport at (still) normal aortic root dimensions.

Sports advice aimed at lowering the burden on the joints is at the level of "common sense" ("A*lthough there have been no trials to investigate the effectiveness of sports limitation to*

avoid joint damage, common sense suggest that activities likely to stress the joints should be avoided.") (Dean, 2007).
In connection with an increased risk of pneumothorax, scuba diving is discouraged.

Conclusions

Level 4	Most guidelines discourage participation in sports involving rapid accelerations and decelerations, sports requiring intensive static exertion and contact sports. Participation in recreational low-to-moderate intensity sports is permitted in most guidelines. Guidelines recommend that children participate as much as possible in normal school gym and outdoor play activities. Participation in intensive sports tests such as the Cooper Test or the Shuttle Run Test is not recommended. D Maron et al, 2004; Maron & Zipes, 2005b; Pelliccia et al, 2005; Pelliccia et al, 2008

Considerations

The international literature contains clear advice regarding the sports participation of patients with Marfan syndrome. On the one hand, these recommendations are based on theoretical considerations and the partly investigated effects of haemodynamic stress on the aortic wall, especially when dilatation and decreased distensibility is already present, and on the other, on retrospective observations concerning the circumstances under which patients developed aortic dissection or rupture. The advice of the ESC and ACC expert panels differ in the details regarding Marfan patients without aortic root dilatation. Advice should be tailored to fit individual needs and with as few restrictions as possible, especially with regards to children. The same sports exercise advice should be followed for non-sports related (daily) activities. In the opinion of the working group, there is no reason to dissuade Marfan patients from participation in normal daily activities (including sexual activity).
National Marfan organisations have an important supporting role to play in disseminating this lifestyle advice.

Recommendations

Advice regarding participation in sports should be tailored to fit individual needs, for example, taking into account the condition of the aorta and the use of anticoagulants.

Caution should be exercised with regard to competitive sports, major peaks of exertion and intensive static exertion.
Participation in recreational low-to-moderate intensity exercise can usually be allowed.

Children should participate as much as possible in normal school gym classes and outdoor play activities. Advice against participation in intensive sports tests such as the Cooper Test or Shuttle Run.

There is no reason to dissuade Marfan patients from participating in normal daily activities (including sexual activities).

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Section 15 Organisation of Care

Introduction

Marfan patient care is organised around Marfan clinics. These centres provide a team of medical specialists with expertise in the area of Marfan syndrome. This section aims to provide an illustration of the requirements that must be met by a Marfan clinic and recommendations for the organisation of diagnosis, monitoring and treatment.

Literature

There is no scientific literature to prove that the care for Marfan patients in a center of expertise is better than elsewhere. Nevertheless, the working group considers that a relatively rare multisystem disorder such as Marfan syndrome requires a multidisciplinary approach by specialists with expertise in the field of Marfan syndrome. A multidisciplinary approach is in line with recommendations in the literature: "*The diagnosis and management of Marfan syndrome requires a multidisciplinary team approach, in view of its multisystem effects and phenotypic variability*"(Dean, 2007). This is endorsed by the patientgroup "Contactgroup Marfan Netherlands".

Out-patient clinics

Each clinic has at least one coordinator. This can be a doctor, but may also be a genetic counsellor or specialist nurse. The care coordinator is responsible for the organisational aspects of the Marfan out-patient clinic and may play a role in providing the patient with information. A Marfan team consists of at least a cardiologist, paediatric cardiologist, cardio-thoracic surgeon, paediatrician, clinical geneticist and an ophthalmologist. A paediatric endocrinologist, orthopaedic surgeon, gynaecologist and one physiotherapist can be part of the team or make contributions on a consultative basis. It is recommended that each Marfan team has a link via the website of the relevant University Medical Centre that clearly shows to whom and how a patient referral should occur and provides details of the coordinator or contact person.

Procedure

Referral

A patient consults the (family) physician with features reminiscent of Marfan syndrome. See also section "Diagnostics". It is recommended that in cases with a strong suspicion of Marfan syndrome (e.g. dilatation or dissection of the aortic root without obvious cause, lens (sub)luxation or a first-degree relative with Marfan syndrome), the patient should be referred to a Marfan clinic. Patients with less specific features of Marfan syndrome are reviewed by the coordinator following referral, who then prepares a treatment plan. The referring physician should have a clear idea of how and to whom a patient should be referred.

The first appointment should take place within 4-8 weeks of referral. If this deadline is not feasible, it is recommended that the patient undergo an ultrasound examination of the heart in a local hospital to exclude serious pathology.

If serious pathology is suspected on the basis of the assessment of the referring physician, then the patient should obviously be referred to either an emergency department or directly to an appropriately qualified specialist.

Diagnosis

In a Marfan clinic, all diagnostic studies necessary for determining a diagnosis are performed in a single day (or part of). In practice, this means: (family)history and physical examination by the clinical geneticist, and examination by a (paediatric)cardiologist and ophthalmologist. Upon adequate suspicion, a blood sample is taken by the clinical geneticist for DNA testing. Although in most cases the results of the DNA tests can be slow (months or longer), at the end of this first visit it is usually possible to provide a statement of the probability that the referred patient has Marfan syndrome. Preferably, this preliminary result is discussed with the patient by the coordinating physician at the end of the day of diagnosis, and confirmed by a letter within 2-4 weeks, with copies to the relevant specialists, referring doctor and GP.

The Marfan team coordinator/clinical geneticist draws definitive conclusions following receipt of the result of the DNA test. The patient is notified in a final interview and the check-up schedule at the Marfan clinic modified, if necessary. This is followed by confirmation in writing to the patient, GP and specialists involved.

If, based on clinical investigations, insufficient evidence is found for a diagnosis of Marfan syndrome, then alternative diagnoses should be considered; see "Differential Diagnosis".

Clinical assessment

See the section "Clinical assessment". The frequency of clinical assessment is determined by the clinical findings. Clinical assessment of children preferably takes place on a single day, in a multidisciplinary setting, with specialists from the Marfan team. In practice, adults only see a cardiologist and, after cardiovascular surgery, a cardio-thoracic surgeon. Assessment by other specialists takes place only on indication. Clear local arrangements are needed for the transfer of a patient from a paediatric cardiologist to a cardiologist. It should be clear at what moment the cardiologist should call in a young person for the first check-up and there should be a clear, written handover. The transition from a paediatric cardiologist to a regular cardiologist is an appropriate moment to offer a young person an appointment with the genetic counsellor/coordinator. The genetic aspects can be discussed and the patient can be informed of the possibility of making an appointment with the clinical geneticist should there ever be a wish to start a family.

Treatment

See sections 6 to 8, in which special attention is devoted to drug treatment, aortic surgery and the treatment of musculoskeletal disorders. Treatment is the responsibility of the treating specialist.

Pregnancy and childbirth

See the section 12 "Pregnancy and Childbirth". The clinical geneticist or coordinator of the Marfan team must tell patients that they should contact the coordinator should they wish to start a family, allowing a multidisciplinary treatment plan to be prepared in the case that the prospective mother has Marfan syndrome. With an already pregnant patient, this treatment plan should be prepared at the earliest possible stage of the pregnancy. The factors included are also listed in the checklist "Pregnancy and Marfan syndrome." During pregnancy, the gynaecologist and the cardiologist are the primary responsible physicians.

Recommendations

Each Marfan team has a coordinator who may be contacted by Marfan patients and referring physicians. The coordinator's contact details are known to patients and referring physicians.

Effort should be made to reach a clinical diagnosis of Marfan syndrome within 3 months of referral by the general practitioner.

It must be clear to referring physicians how and to whom the referral should be made; a clear link on the website of the University Hospital is recommended.

Check-ups are dictated by the abnormalities found.

During the transition from paediatric cardiologist to regular cardiologist, an appointment should be made with the clinical geneticist.

Pregnancy in a Marfan patient requires multidisciplinary care, coordinated by a gynaecologist and cardiologist.

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Section 16 Patient Information

Introduction

In many cases, the first confrontation with a (possible) diagnosis of "Marfan syndrome" will provoke considerable uncertainty in a patient and/or in his or her immediate family. It is common that those familiar with the Internet almost immediately launch on a veritable treasure hunt using "Marfan" and "Marfan syndrome" as search terms. Fortunately, there is now so much useful and readily available information that this initial information hunger can be partly satisfied. However, translation of the general information found on the Internet to their personal situation still appears to be difficult for many patients, and brings with it uncertainty and an unclear picture of the status and future of life with Marfan syndrome.
The website of the Contactgroup Marfan Netherlands (www.marfansyndroom.nl) offers a wealth of accessible information on a wide range of subjects. The Contactgroup can be easily reached for all questions arising from the first confrontation with Marfan syndrome, using a variety of channels. When a patient requires "peer support", the treating physician may refer him/her to the Contactgroup.

Diagnosis

It is clear that provision of information by the medical team regarding the process leading up to a final diagnosis can be of great importance to a patient. In addition to examination of the patient, examination of relatives may also be essential. Any advice is usually insufficient to remove (all) uncertainty in the patient and relatives, but it is usually possible to provide a more acceptable perspective.
It is important that patient information clearly explains the agreements between the medical team and the patient and/or family. This concerns both agreements on the specific roles of medical team members and the family doctor, and on the coordination of care. It is also important that the patient is aware of the length of time required to make the diagnosis. What can be expected from the medical team during the course of the diagnostic process, in terms of treatment and counselling, should also be clear.

Monitoring and treatment

During the course of the monitoring and treatment of a patient with Marfan syndrome, a phased, timely and targeted provision of advice, in everyday language, to the patient and/or the immediate family must remain a central priority of practitioners in the medical team.

The transition from "diagnosis" to "monitoring and treatment"

Just as in the diagnosis phase, the patient and/or relatives should be informed of agreements with the medical team practitioners. This is especially true if the team is different to that during the diagnosis phase. This concerns agreements on the specific roles of medical team members and the family doctor, and on the coordination of care. The patient must receive clear information on who the care coordinator is and who to approach during a specific course of treatment. What can be expected of the medical team during further stages, in terms of treatment and counselling, should also be clear.

Regular check-ups

Due to cardiac problems, Marfan patients should receive regular check-ups (every six months to once every few years). It is desirable that patients and families, through targeted and timely information, remain aware of the need for regular assessment. Being able to rely on one coordinating individual in a research institute medical team or Marfan clinic is not only a clear desire of individual Marfan patients, but can also represent an important stimulus to medically appropriate monitoring and compliance. This contact person can also play a coordinating role in informing the patient of results of examinations.

Coordinating information on medical consequences

Marfan patients express a clear need for practical advice and information. Besides the obvious need for information on the implications of cardiac and eye diseases, there is certainly a need for information on the implications with respect to muscle problems, orthopaedic abnormalities, dural ectasia, lung defect(s) and impact on daily life. Practical advice on everyday life is especially important.

The above-mentioned coordinating contact individual in the medical team can play an essential role in providing information.

Advice on lifestyle

In connection with cardiac and lung problems in Marfan patients, issues such as hypertension and smoking are important and require attention. The treating specialist can play a role by, for example, giving advice on lifestyle, by referral for help with stopping

smoking and/or treatment for hypertension. Advice on lifestyle is also possible with regard to ophthalmic and orthopaedic problems.

Sports advice (also see section 14)
The treating specialist may refer a patient to a sports physician if there is a desire for (intensive) sports participation. The sports physician can advise the patient on which branch of sport is suitable, based on an individual situation. It is recommended that the patient always seek the advice of a cardiologist before he/she actively participates in sport.

Psychosocial aspects

General
It can not be stressed enough that caregivers should pay special attention, in the form of advice, to the psychosocial aspects of Marfan syndrome. Due to the complexity of the symptoms, those aspects are often difficult for the patient to distinguish. An additional aggravation of the situation is represented by the incurable nature of Marfan syndrome. Despite the psychosocial burden of disease, the experience of the Dutch patient organisation suggests that Marfan patients are often very positive about life.
Signals that may indicate excessive physical and/or psychological stress on the patient, his or her partner and/or family should be noted by the care coordinator. The care coordinator can help a patient by offering a listening ear and more practically, by referring the patient to a psychologist or social worker.
Incidentally, the family doctor also has an important to role play in identifying excessive psychosocial stress.

Young children, their parents and the family
The psychosocial care of young children with Marfan syndrome, their parents and the family receives considerable attention at out-patient clinics for Marfan children. In other situations, there is an urgent need to provide the parents with the necessary information. Regular feedback should be sought from the young Marfan patient and possibly from other children in the family.

Adolescence
Psychosocial problems, especially in (pre)adolescents, may result from the sometimes extreme height growth and the physical appearance, but may also be caused by the impact of treatments such as hormonal or surgical length reduction or cardiac surgery. Adolescents may become socially isolated, and adolescent rebellion can also lead to denial

of the importance of regular check-ups. The care coordinator should be aware that during contact with the patient in this particular life phase (approaching autonomy), special attention should be paid to providing information on and stressing the importance of check-ups and compliance, on providing lifestyle advice and confronting any psychosocial problems. Any problems that may arise in school (introduction of necessary adaptations to furniture and/or classroom aids, changes to gym lessons, necessary additional educational support) can be (partly) overcome by targeted advice by the treating physician.
The transition from adolescence to adulthood requires that the care coordinator be prepared to provide extra attention and advice.

The older Marfan patient (50+)
Information on the consequences of specific symptoms that the older patient with Marfan syndrome may face is desirable. This information should preferably be available at the regular (annual) check-ups, and should be provided by the care coordinator.

The partner of a Marfan patient
The partner of a Marfan patient can play an important role in the process of aftercare. It is desirable that a patient's partner is involved in the provision of any advice. This is particularly the case if it appears that the partner exhibits a (great) need for psychosocial support and advice.

Psychosocial support
A patient with Marfan syndrome will have adapt to circumstances, given the physical constraints that the disease entails. This can be expressed in the choice of further education, career or the distribution of a limited energy reserve over (daily) activities. Some patients also have problems with their appearance or may encounter misconceptions amongst those around them. Due to chronic fatigue and other symptoms caused by Marfan syndrome, the patient will have to regularly call on those around them.

The working environment
The working environment can reveal the limitations of Marfan patients (e.g. endurance, joint strength). To what extent the (working) environment should be informed of these limitations and their cause can be a serious dilemma for Marfan patients. In such situations, the specialist treating the patient can recommend consulting the family or company doctor for help and advice.

Insurance

The specialist(s) treating a patient can provide further information to the insurance company doctor when a patient experiences problems taking out insurance.

Recommendations

Providing Marfan patients with good advice during diagnosis, monitoring and treatment is essential to both the success of the medical care and well-being of patients. In the field of advice provision, the following recommendations can be made.

After diagnosis

- Ask how the patient and/or family experienced the medical team's approach in the phase prior to the diagnosis.
- Assess to what extent the patient and relatives have processed and accepted the diagnosis.
- Ascertain whether the need for further investigations in the family is understood by the patient and relatives and whether sufficient explanation was given.

During control and treatment:

- Introduce a single care coordinator to act as a contact for the patient and his/her parents.
- Make the patient aware of how responsibilities are divided amongst the treating specialists. In the event that a Marfan patient has a prosthetic valve or a valve abnormality, the patient should be made aware of the increased risk of endocarditis and that profylaxis for endocarditis is indicated. It is of great importance that paradontitis and caries be prevented. The dentist and/or dental hygienist play an important role in providing advice. The NHG Endocarditis Profylaxis Guideline clarifies other circumstances under which profylaxis for endocarditis is indicated.
- Provide advice on lifestyle and sports advice, if relevant.
- Pay special attention to psychosocial issues including:
  - Specific issues in relation to age;
  - Family and friends;
  - Employment and insurance.

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A general website with information about Marfan syndrome and links to external sites: www.marfansyndroom.nl

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NHG Guideline Endocarditis profylaxis oktober 2008 (first revision december 2009): http://download.nhg.org/FTP_NHG/standaarden/FTR/Endocarditisprofylaxe_text.html

Prevention Bacterial Endocarditis 2008 (RP54): http://www.webshop.hartstichting.nl/producten/producten.aspx?CatID=71&pID=3765

Appendix 1 Clinical Questions

Diagnostics

- What are the symptoms that indicate Marfan syndrome and which diagnostic test is appropriate?
- What is the policy in relation to a newborn with a 50% risk of Marfan syndrome?

Differential Diagnosis

- What alternative diagnoses should be considered and what are the criteria?

Family studies

- How should family studies be conducted, where, in which family member and at what moment?

Pregnancy and childbirth

- What are the risks of pregnancy and childbirth in a patient with Marfan syndrome?
- Type and frequency clinical assessment during pregnancy.
- When and how should a birth take place?

Prenatal diagnosis/preimplantation diagnosis

- What are the possibilities for prenatal diagnosis/preimplantation diagnosis, and are there specific risks?

Clinical assessment

- Frequency and nature of clinical assessment, as applicable to both adults and children.

Treatment

- What is the effect of drug treatment on the dilatation of the aortic root?
- What is optimal moment for preventive aortic surgery in adults/children?
- Can brace treatment, compared with the natural disease course, prevent surgical intervention?

Lifestyle

- Does participation in (top)sport and certain other activities lead to greater complications?

Patient information

- Which information is important for patients with Marfan syndrome?

Appendix 2 Characteristics of Marfan Syndrome

	Gent II criteria (Loeys et al, 2010)	Gent I criteria (De Paepe A. et al, 1996)
Facial features	+	+
dolichocephaly	+	+
enophthlamos	+	+
downward slanting palpebral fissures	+	+
malar hypoplasia	+	+
retrognathia	+	+
high and narrow palate	-	+
dental crowding	-	+
long face	-	-
Skeletal features		
arachnodactyly (positive thumb and wrist sign)	+	+
pectus carinatum	+	+
pectus excavatum	+	+
chest wall asymmetry	+	-
hindfoot deformity	+	+
pes planus	+	+
protrusio acetabuli	+	+
long arms and legs	+	+
reduced elbow extension	+	+
scoliosis	+	+
thoracolumbar kyphosis	+	+
joint hypermobility	-	+
umbilical sign	-	-
Cardiovascular features		
aortic root dilatation or dissection	+	+
mitral valve prolapse	+	+
tricuspid valve prolapse	-	-
pulmonary artery dilatation	-	-
aortic dilatation or dissection distally from the aortic root	-	-
Ophthalmologic features		
lens(sub)luxation	+	+
myopia	+	+
increased globe length	+	-
Hypoplasia of the iris or ciliary muscle	+	-
corneal flattening	+	-
cataract	-	-
retinal tears	-	-
Family history		
first degree family member with Marfan syndrome	+	+
Other features		
pneumothorax	+	+
apical blebs	-	+
emphysema	-	-
dural ectasia	+	+
striae	+	+
Recurrent inguinal herniae	-	+
recurrent umbilical herniae	-	+
recurrent incisional herniae	-	+
reduced body muscle and fat	-	-
tall stature	-	-

+ feature is part of the criteria
- feature is not part of the criteria

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Appendix 3 Summary of Focus Group Meeting

Five people participated in the Marfan guideline focus group, three of whom themselves have Marfan syndrome, two have a child with Marfan syndrome, and one Marfan patient also has a child with Marfan syndrome. Three patients provided a report of their experiences, based on a set of prepared questions. The age at which Marfan syndrome was discovered ranged from 3 to 60 years. Several patients lost immediate family members prior to diagnosis, probably due to the symptoms of Marfan syndrome. The rapidity of diagnosis varied widely, and seemed to particularly depend on the familiarity with Marfan syndrome of the attending physician. There is room for improvement regarding the familiarity of the medical profession with Marfan syndrome.

The following points were discussed:

Communication and Marfan syndrome – have all the implications been clearly explained?
All participants expressed dissatisfaction with this aspect. The consequences for cardiology were clearly explained, and eye defects were explained briefly. However, the other abnormalities such as joint/muscle complaints, dural ectasia, lung disorders and implications for daily life received little or no explanation. The bulk of their knowledge was derived from the patient group website and from conversations with others with Marfan syndrome.

Have you heard about the do's and don'ts of Marfan syndrome?
Some patients received no advice, others were told that they should avoid strenuous exercise and endurance sports. They all indicated that they have received some information regarding the theoretical risks, but feel that the translation into practical advice for everyday life is lacking. However, the individual circumstances of the patient should not be overlooked, and individual limitations will vary from person to person.

What is your experience of the organisation of care and the collaboration between disciplines?
The patients were satisfied with the Marfan clinics in the Netherlands, and also preferred to be treated there. They did feel the lack of one central individual. Specialists give conflicting advice on what to do or what not to do.

How was the transition from paediatrician to several specialists in adulthood experienced?
The transition from the safe environment of a children's clinic to the anonymous,

impersonal environment of the adult clinic is a huge step. In the children's clinic, you are called in as necessary, but as an adult you have to suddenly do everything yourself. They feel the lack of a transitional period in which children are guided towards independence as a patient, and they would like to see transition nurses integrated into the Marfan clinic.

What are the typical symptoms in an older Marfan patient?
The distinction between age-related and Marfan-related ailments is currently unclear to both doctors and patients. This is an issue that they would like to see researched.

What are the good points of care?
Everyone is very satisfied with the children's clinics.

What are the main areas for improvement?
(Parents of) patients would also like to receive a copy of the letter sent to the GP following a visit to a specialist.
The cooperation between the specialists would be improved by appointing a single coordinator, generating the impression that there is an overview of all problems.
Some patients see a different ophthalmologist and cardiologist each time. Why can't this just be the same each time?
Greater attention should be paid to complaints relating to body regions/organs other than the heart, so that the patient can be referred to another specialist, if necessary. Complaints are discussed but do not lead to sufficient action or are not taken seriously.
There is too little preparation prior to a consultation, even by interns. Perhaps doctors could prepare a summary of all important information from the medical files.
Just as in the children's clinic, adults also prefer that all investigations take place on the same day, as much as possible.

Are there any questions/points that have not been addressed?
The partners of Marfan patients play an important role in the aftercare, but now are not sufficiently involved. If the partner is present during a consultation, he or she can also help ensure that all necessary information is available, both during and after the consultation.

<u>Improvements at a glance:</u>

- Improved information on what Marfan syndrome entails; the do's and don'ts are not communicated consistently.
- One central coordinator, above all specialists, is highly desirable.
- Preferably - only treatment by doctors in a Marfan (outpatient) clinic.

- The transition from child to adult care is too abrupt. A transition nurse is necessary to smooth this transition.
- Patient's partners should also be involved in the aftercare.
- Improved syndrome recognition by 'regular' doctors; for example, via a magazine read by many doctors.

Appendix 4 On behalf of - Financial support - Acknowledgements

On behalf of

The guidelines were developed on behalf of the Dutch Society of Paediatrics, Dutch Ophthalmological Society, Netherlands Association for Cardio-Thoracic Surgery, Dutch Society of Obstetrics and Gynaecology, Dutch Orthopaedic Association, Dutch Society of Clinical Genetic Diagnostic Laboratories and Netherlands Society of Cardiology.
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