Radiological imaging in the investigation of Marfan syndrome

Rigmor Lundby

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Faculty of Medicine, University of Oslo
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Department of radiology and nuclear medicine
Division of diagnostics and intervention
Oslo University Hospital
Norway

Contents

1. Acknowledgements

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During these years I have been employed as a research fellow at the University of Oslo and engaged part time as a practitioner of radiology at the Neuroradiology unit, Department of Radiology and Nuclear Medicine, Oslo University Hospital, Rikshospitalet.

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2. List of papers

This thesis is based on the following papers, which will be referred to by their Roman numerals:

I.   Rand-Hendriksen S, Lundby R, Tjeldhorn L, Andersen K, Offstad J, Semb SO, Smith H-J, Paus B, Geiran O. Prevalence data on all Ghent features in a cross-sectional study of 87 adults with proven Marfan syndrome. Eur J Hum Genet 2009;17:1222-30. Erratum in Eur J Hum Genet 2009;17:1526

II. Lundby R, Rand-Hendriksen S, Hald JK, Lilleås FG, Pripp AH, Skaar S, Paus B, Geiran O, Smith H-J. Dural Ectasia in Marfan Syndrome: A Case Control Study. AJNR 2009;30:1534-40

III. Lundby R, Kirkhus E, Rand-Hendriksen S, Hald JK, Pripp AH, Smith H-J. CT of the hips in the investigation of protrusio acetabuli in Marfan syndrome. A case control study. Eur Radiol 2011;21:1485-91

IV. Lundby R, Rand-Hendriksen S, Hald J, Pripp AH, Smith H-J. The pulmonary artery in Marfan syndrome patients. A cross-sectional study. (Submitted)

3. Abbreviations

AM = anterior meningocele

AP = anteroposterior

CI = confidence interval

CT = computed tomography

CTA = computed tomography angiography

CWD = circle-wall distance

DE = dural ectasia

DSD = dural sac diameter

DSR = dural sac ratio

FBN1 = human gene encoding the protein fibrillin 1

HRCT = high resolution computed tomography

ICC = inter class correlation coefficient

MASS syndrome/MASS phenotype = requires at least two of the following manifestations: myopia, mitral valve prolapse, aortic root diameter at the upper limits of normal for body size, skin stretch marks (striae), and minor skeletal features of Marfan syndrome

MDCT = multi detector computed tomography

MFS = Marfan syndrome

MRI = magnetic resonance imaging

MRA = magnetic resonance angiography

PA = protrusio acetabuli

PACS = picture archiving and communication system

ROC = receiver operating characteristic

R-R interval = interval between heartbeats

SD = standard deviation

TE = echo time

TEE = transesophagial echocardiography

TGFBR1 = human gene encoding the protein transforming growth factor, β receptor 1

TGFBR2 = human gene encoding the protein transforming growth factor, β receptor 2

TR = repetition time

VBD = vertebral body diameter, measured at mid-corpus level

4. Introduction and background

Marfan syndrome (MFS) is an autosomal dominant disorder of connective tissue. Life expectancy is generally reduced in MFS patients, mainly due to progressive dilation and dissection of the aorta. Other manifestations include dislocation of the lens and skeletal deformities. Early diagnosis, follow-up, and treatment are important to prolong life and reduce disability.

"Radiological Imaging in the Investigation of Marfan Syndrome" is a spin-off project derived from the "Norwegian Marfan Study", a collaborative project between the Norwegian user organisation ("The Norwegian organisation for Marfan Syndrome (MFS) and other Marfan-like disorders"), TRS - a national resource center for seven rare disorders, and co-workers from different hospital departments, representing specialists in thoracic and vascular surgery, cardiology, ophthalmology, radiology, medical genetics, clinical chemistry and physical medicine and rehabilitation at Oslo University Hospital.

The main project was initiated by Svend Rand-Hendriksen, MD, PhD, who aimed to explore the MFS genotype and phenotype in accordance with the diagnostic system used at that time, the "Ghent 1 criteria" (1). He also intended to "investigate the prevalence of the phenotypic features and their consequences for perceived health-related quality of life" (2).

In the "Norwegian Marfan Study" all patients were assessed for all parts of the diagnostic system, the "Ghent 1" criteria, by the same group of physicians (Table 1). Medical imaging technologies have become immeasurably important tools in many medical disciplines; so also in the diagnostic process of the pleiotropic disorder MFS. The need for radiological imaging examinations was the starting point of this project. Radiological imaging according to the Ghent criteria is required to assess dural ectasia, scoliosis, spondylolisthesis, protrusio acetabuli, calcification of the mitral annulus, pulmonary artery dilatation, and apical blebs in the lungs. In addition radiological imaging gives better visualization of the aortic arch and descending aorta than echocardiography. Different radiological methods have been used in the diagnostic process of MFS, and there is an ongoing discussion on which methods are necessary to include in this process. Through this thesis, I hope to participate in the debate on which radiological methods are important in the diagnostic process of MFS.

Table 1. Diagnostic criteria for Marfan syndrome (MFS) according to the Ghent 1 nosology

	Major criteria	Criterion for involvement
Skeletal	*Requires four of the eight manifestations listed below* Manifestations • Pectus carinatum • Pectus excavatum requiring surgery • Reduced upper to lower segment ratio < 0.85 or arm span to height ratio greater than 1.05 • Wrist and thumb signs • Scoliosis of > 20° or spondylolisthesis • Reduced extension at the elbows (< 170°) • Medial displacement of the medial malleolus causing pes planus • Protrusio acetabuli of any degree	*Requires two of the eight manifestations in the left column or one manifestation plus two of the four minor criteria listed below* Minor criteria • Pectus excavatum of moderate severity • Joint hypermobility (Beighton score ≥ 4) • Highly arched palate with crowding of teeth • Facial appearance (dolicocephaly, malar hypoplasia, enopthalmos, retrognathia, down-slanting palpebral fissures)
Ocular	• Ectopia lentis	*Requires two of the following three minor criteria* Minor criteria • Abnormally flat cornea (< 41,5 dioptres) • Increased axial length of the ocular globe (>23,5 mm) Hypoplastic iris or ciliary body
Cardiovascular	• Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva • Dissection of the ascending aorta	*Requires the presence of at least one major criterion or one minor criterion* Minor criteria • Mitral valve prolapse with or without mitral valve regurgitation • Dilatation of the main pulmonary artery in the absence of valvular or peripheral pulmonic stenosis or any other obvious cause below the age of 40 years • Calcification of the mitral annulus before the age of 40 years • Dilatation or dissection of the descending thoracic or abdominal aorta below the age of 50 years
Pulmonary	None	*Requires at least one minor criterion* Minor criteria • Spontaneous pneumothorax • Apical blebs
Skin and integument	None	*Requires at least one minor criterion* Minor criteria • Striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy or repetitive stress • Recurrent or incisional hernia
Dura mater	• Lumbosacral dural ectasia	None
Genetic	• Having a parent, child or sib who meets these diagnostic criteria independently • Presence of a mutation in *FBN1* known to cause the Marfan syndrome • Presence of a *FBN1* haplotype around *FBN1,* inherited by descent, known to be associated with unequivocally diagnosed Marfan syndrome in the family	None

4.1 Historical background for the MFS diagnosis

In 1896, the Parisian pediatrician Antoine Marfan, described Gabrielle P, a 5 year old girl who was unusually tall, and had long and slender fingers and toes. This was the first description of the syndrome which was later named after him (3). However, whether the girl actually was affected by Marfan syndrome or not, has never been clarified.

In 1956, MFS was described by Victor A. McKusick as an example of "heritable disorders of connective tissue" (4), and in 1979 criteria for MFS were proposed by Pyeritz and McKusick ("The Marfan syndrome: diagnosis and management") (5). A committee of international consultants suggested standards for the diagnosis of common heritable disorders of connective tissue in 1986, also including MFS (the Berlin nosology) (6).

In 1991, a mutation in the gene encoding for fibrillin (*FBN1*) was reported as the cause of MFS for the first time (7). One hundred years after the first description of this disease, in 1996, the revised criteria for MFS (Ghent 1) were presented by DePaepe et al. in the article "Revised diagnostic criteria for the Marfan syndrome" (1) (Table 1).

In 2010, the most recent nosology for MFS was published by Loeyz et al. in the paper "The revised Ghent nosology for the Marfan syndrome" (8) (Ghent 2). This nosology will be briefly presented only, since all examinations and evaluations in the "Norwegian Marfan study" were performed according to Ghent 1.

4.2 Etiology

The only gene mentioned in the Ghent 1 criteria for MFS is the *FBN1* gene at 15q21 (1). There are, however, found numerous different mutations in this gene in different MFS patients, and it is said that many families carry their own private mutation (9;10). *FBN1* mutations are found in individuals fulfilling the Ghent 1 criteria for MFS as well as in persons not fulfilling the Ghent 1 criteria (10;11). *FBN1* mutations can lead to a variety of conditions that are related to MFS, including the MASS phenotype (myopia, mitral valve prolapse, aortic dilatation, skin and skeletal involvement), familial ectopia lentis, familial Marfan-like habitus, familial thoracic aortic aneurysms and dissections, Weill–Marchesani syndrome and Shprintzen–Goldberg syndrome.

All persons exhibiting an *FBN1* mutation independent of whether they fulfill the Ghent criteria or not are said to belong to a "Type 1 fibrillinopathy" (12). Hundreds of different mutations have been identified till now, and according to Stheneur et al. the great majority

(79.1%) of all *FBN1* mutations described today (more than 1750, data not published) come from the European laboratories and especially Western Europe (13).

In addition to the finding of different fibrillin 1 mutations in Ghent positive patients, mutations in *TGFBR1* and *TGFBR2* have recently been reported in individuals fulfilling the Ghent 1 criteria (2;14;15). These patients (previously given the diagnosis MFS 2) are now defined as having Loeys-Dietz syndrome.

Mutations of *FBN1* may cause abnormal microfibrils, and either alone or in association with elastin in the elastic fibers, these abnormal microfibrils can induce fragmentation of elastic fibers, and impairment of elastic tissue homeostasis. Manifestations in the connective tissue like ectopia lentis, protrusio acetabuli and dural ectasia can be explained by these changes in the elastic tissue.

Mutation of *FBN1* also affects the regulation of tissue growth factor signaling (TGF-β signaling), which is related to the pathogenesis of bone overgrowth, pulmonary manifestations, valve changes, and aortic dilatation (16-19). Research on mouse models has revealed that dysregulation in TGF-β signaling is important in the genesis of different developmentally and acquired states of elastic tissue deficiency in MFS. Part of the control of fibrillin-1 over connective tissue homeostasis is mediated by limiting activation of TGF- β. Fibrillin-1–deficient lung tissue has been shown to have increased presence of activated TGF-β (16).

4.3 Manifestations and Diagnosis

As already stated, MFS includes manifestations in many organ systems, with diverse features in different organs arising from a single mutation. There are several different phenotypes of this disease, and in the "Norwegian Marfan study" 87 patients fulfilled the Ghent 1 criteria in 56 different ways.

In the *cardiovascular system,* progressive dilatation of the aorta, usually maximal at the sinus of Valsalva is associated with aortic valve incompetence, and aortic dissection or rupture. The aortic pathology represents the main cause of morbidity and mortality in Marfan syndrome (20). Other cardiovascular signs are mitral valve prolapse, with or without regurgitation, descending aorta dissection, and dilatation of the main pulmonary artery. Dilated cardiomyopathy in the absence of severe valvular dysfunction may also be found (21).

In the *musculoskeletal system,* tall stature, and long arms, legs, fingers and toes are common, (dolichostenomelia, arachnodactyly). Pectus excavatum or carinatum, scoliosis of the vertebral column, and protrusio acetabuli are also among the features.

In the *ocular system,* ectopia lentis is the most serious affection, but myopia and retinal detachment may also be present.

In the *lungs,* apical blebs may be found, and pneumothorax is a possible complication to this. In the *skin and integument,* striae not related to pregnancy, and hernias are seen. In the *nervous system*, dural ectasia is found in a high percentage of patients.

The diagnosis of MFS is based on the identification of a combination of the manifestations listed in Table 1. Confirmation of the diagnosis in an individual requires the presence of major clinical manifestations in at least two organ systems associated with involvement of a third organ system. In the presence of an *FBN1* mutation known to cause MFS, or in relatives of an affected proband, major involvement of one organ system and involvement of a second organ system confirms the diagnosis (1).

In the revised Ghent criteria published in 2010 (Ghent 2 criteria) more weight is given to aortic root aneurysm/dissection and ectopia lentis. The combination of ectopia lentis and aortic root enlargement/dissection are sufficient for diagnosis of MFS alone. Features in the cardiovascular, ocular, skeletal, dura, integument, and skin, contribute to the diagnosis as systemic signs. Some findings are weighted more than they were in the Ghent 1 criteria, for instance protrusion of the acetabulum; others are weighted less, for instance dural ectasia. Pulmonary artery dilatation is not counting as a sign of MFS according to these new criteria (8).

The Ghent 2 nosology was published subsequent to the time when we completed clinical examinations and most of the analysis of this study. Our study population was diagnosed according to the Ghent 1 nosology.

4.4 Epidemiology

4.4.1 Prevalence

The prevalence of MFS is difficult to estimate because the reported prevalence is dependent on the inclusion criteria being used for the diagnosis. Changing diagnostic systems have entailed that some patients fulfilling the diagnosis according to one system, do not fulfill another. Radonic et al. examined patients for both Ghent 1 and Ghent 2 criteria, and some of the patients fulfilled the Ghent 1 but not the Ghent 2 criteria (22). Some of the signs for MFS also do not develop until adolescence or adulthood, and this makes the diagnosis even more difficult to assess.

A study in Scotland published in 1994, found a minimal prevalence of MFS to be 1:14,217 (23). In 2007 von Kodolitsch et al. reported an estimated prevalence for MFS of 1 in 5,000 individuals (24), while in 2008 Rybczynski et al. reported a prevalence of "MFS and Marfan-like syndromes" to be 7 in 100,000 people (25).

Men and women are said to be affected equally often by MFS (24), and approximately 25% of cases are caused by de novo mutations (26). Gray found that 26.7% of their MFS patients were de novo mutations (23).

4.4.2 Survival

Mean age at death (± SD) was found to be 41 (± 18) years in a study by Silverman et al., published in 1995 (27). This was significantly increased compared with mean age at death in 1972 which was 32 (± 16) years (p = 0.0023) (28).

4.4.3 Treatment

Treatment decisions concerning MFS depend on manifestations in the single patient. Marfan syndrome and Marfan-related syndromes are diseases which may involve several organ systems and therefore require coordinated medical care from specialists in different areas. Complete management requires team work, including a geneticist, cardiologist, ophthalmologist, orthopedist, and cardiothoracic surgeon, and a radiologist.

When the maximum diameter of the aorta exceeds 5.0 cm, surgical repair is needed. When the rate of increasing aortic diameter approaches 1.0 cm per year, or progressive aortic regurgitation occurs, surgery is also needed. Patients with a family history of early dissection of the aorta may need more aggressive therapy (7). In the latest guidelines for treatment of

patients with thoracic aortic disease, it is recommended that a ratio between the maximal cross-sectional area in square centimeters of the ascending aorta or root and the patient's height in meters should be used; if this ratio exceeds 10, surgical repair is reasonable. This is because shorter patients have dissection at a smaller aortic size, and 15% of patients with Marfan syndrome have dissection at an aortic diameter less than 5.0 cm (29).

Use of β-adrenergic blockade to reduce hemodynamic stress on the proximal aorta in Marfan syndrome was first suggested in 1971 (21), and in a study published in 2006 by Ladoceur et al., where treatment with β-adrenergic blockade was tried on children, there was a trend towards lower mortality, less preventive surgery for aortic dilatation, and fewer cases of dissection (30).

Losartan is an angiotensin II type 1 receptor blocker, and this substance was found to be potentially useful in MFS because it lead to antagonism of TGF-β in animal models of chronic renal insufficiency and cardiomyopathy (31). In a small observational study using losartan in children with severe MFS, preliminary results on aortic dilatation inhibition have been promising (32). The COMPARE study (COzaar in Marfan Patients Reduces aortic Enlargement) is an open-label, randomized, controlled trial with blinded end-points. Treatment with losartan will be compared with no additional treatment after 3 years of follow-up (22).This has yet to be done.

4.5 Radiology in MFS

 To image all the "radiological" features of MFS according to the Ghent 1 criteria, we did the following examinations.

- MRI (or CT) to assess the ascending aorta (examined also by echocardiography), descending aorta and pulmonary artery
- MRI (or CT) to assess dural ectasia and spondylolisthesis in the lumbosacral region
- scout view from CT to assess scoliosis
- CT to assess protrusio acetabuli
- HRCT to assess apical blebs in the lungs, and calcification of the mitral annulus

4.5.1 Imaging of the ascending aorta and pulmonary artery

The ascending aorta is an important structure to examine in this patient group to verify or exclude dilatation and dissection, and different methods have been used in the diagnostic process.

Transthoracic echocardiography is commonly used in the examination of the ascending aorta. In 1979 Pyeritz and McKusick wrote: "Echocardiography has greatly enhanced the detection of the cardiovascular abnormalities, and improved both diagnosis and management of MFS" (33). Weaknesses of this method are high dependability on appropriate acoustic window and skilled operator, and inability to visualize the descending aorta. The descending aorta may be imaged in detail with transesophagial echocardiography (TEE), but this is a more invasive and less available method.

Today, contrast-enhanced computed tomography (CT) is the most commonly used radiological method for imaging of the aorta. CT imaging has been used in many years as a tool for the diagnosis of thoracic aortic diseases, and it has the advantages of being available in most hospitals. This method is exact in displaying details from aorta, and the examination is executed in a short time. CT of the ascending aorta as opposed to echocardiography can depict both thoracic aortic disease, and other diseases that can mimic aortic disease. Especially after intervention on the aorta CT is preferred to detect asymptomatic postprocedural leaks or pseudo aneurysms, because of the presence of metallic closure devices and clips (29). Historically CT images were generated in the axial or transverse plane, orthogonal to the long axis of the body. However, non-gated axial CT examinations of the chest do not take into account the obliquity of the aorta, nor the systolic expansion or the non axial movements during the cardiac cycle (34). Modern multi detector CT (MDCT) scanners have revolutionized medical imaging. Imaging with isovolumetric voxels enables reformations in any plane without loss of spatial resolution, and combined with ECG-trigging, true short axis depiction of any part of the aorta or pulmonary artery is possible without pulsatory artefacts, allowing a more exact measurement of either systolic or diastolic vessel diameter or vessel cross-sectional area. Vessel tortuosity is easily shown by three-dimensional (3D) reconstructions.

MR imaging is a good alternative to CT in imaging of the aorta and pulmonary artery. Being free of ionizing radiation, it should be the method of choice in children and when repeated examinations are indicated, especially in young patients. Drawbacks of the method as compared to echocardiography and CT are cost and less availability. There are several MR methods available for imaging of the aorta and pulmonary artery. ECG-triggered two-dimensional (2D) "black blood imaging" using non-enhanced spin-echo (SE) or turbo spin-echo (TSE) pulse sequences may be performed with or without breath-holding (to eliminate respiratory artifacts). These 2D techniques have the advantage of showing the vessel wall, including vessel wall thickening due to inflammation. 3D gradient-echo (GRE) techniques are generally faster and allow true short axis reformations of vessel lumina or 3D angiographic reconstructions. Both contrast-enhanced and non-enhanced methods are available. Contrast-enhanced 3D MR angiography (MRA) with breath-hold but without ECG-trigging, is superior in visualizing the entire aorta with side-branches, while the somewhat slower non-enhanced 3D steady state techniques such as trueFISP with ECG-trigging and respiratory gating with navigator echo, allow high resolution short axis depiction of the great thoracic vessels free of pulsatory blurring.

According to a publication in 1996, CT had a sensitivity and specificity of 100% for identification of aortic dissection, while transesophageal echocardiography (TEE) and MR imaging both had a sensitivity of 100% and specificity of 94% (35). The authors concluded that CT, TEE and MR imaging are all valuable methods in the detection of thoracic aortic dissection. However, they found that for the assessment of the supraaortic arterial branches, CT was superior (35).

In 2005, Milewicz et al. claimed that "the initial evaluation of an individual with MFS should include an echocardiogram to assess the ascending aorta and cardiac valves" (36). They emphasized, however, that the results of echocardiography are dependent on the sonographer and the equipment, and that spiral thin-slice CT angiography (CTA) or MR angiography (MRA) with 3D reconstructions are precise, and should be used if echocardiography does not provide good quality images of the aorta. They recommended routine CTA or MRA of the entire distal aorta if the descending thoracic aorta is large or has dissected.

In 2010, Hiratzka et al. ("Guidelines for the Diagnosis and Management of Patients With Thoracic Aortic Disease 2010") still recommended echocardiography as the imaging modality

of choice as a start in the diagnostic process of the cardiovascular system in proposed MFS patients, and also in the follow up of the aortic sinus of Valsalva if the diameter is stable. They stress, however, that definitive identification or exclusion of thoracic aortic disease requires dedicated aortic imaging, and that selection of the most appropriate imaging study may depend on patient-related factors like hemodynamic stability, renal function, contrast allergy, and institutional capabilities. Transthoracic echocardiography has according to Hiratzka et al. a sensitivity of 77% to 80%, and a specificity of 93% to 96% for identification of proximal aortic dissection (29).

The Ghent 1 criteria from 1996 stated that echocardiography, CT or MRI may all be used to diagnose dilatation of the aortic root or pulmonary artery diameter, while dissection should be documented by contrast angiography, TEE, CT or MRI (1). English-language reports on the diagnosis of thoracic aortic dissection by TEE, helical CT, or MRI were identified from electronic databases by Shiga et al., 2006. Sixteen studies involving 1139 patients were selected. Sensitivity, specificity, and positive and negative likelihood ratios were pooled in a random-effects model. Pooled sensitivity (98%-100%) and specificity (95%-98%) were comparable between the three imaging techniques (37).

For both contrast-enhanced CT, conventional angiography and MRI consideration should be given to patients with reduced renal function. Iodinated contrast media injection in CT examinations and conventional angiography may induce nephropathy. Gadolinium based contrast agents, used for MRA, imply a risk of nephrogenic systemic fibrosis (29).

4.5.2 Imaging of the lumbosacral column and dural sac

Dural ectasia (DE) is a major criterion for MFS in the Ghent 1 nosology, and is one of the systemic signs of Ghent 2. It is present in a high percentage of patients with MFS. Several articles have been published on how to diagnose this feature.

Conventional radiography was the first method where signs of DE could be found, and as early as in 1958, Nelson et al. reported posterior scalloping seen on a conventional radiograph of the lumbar region of an MFS patient; he stated that "this widening of the spinal canal is different from other causes of spinal canal enlargement because it has different stigmata, and absence of neurological abnormalities"(38). In 1989, Janjua MZ and Muhammad F measured the vertebral body diameter and the estimated dural sac diameter on sagittal, conventional

radiographs in normal persons, and calculated the proportion between these measurements, the C/B (canal/vertebral body) ratio. They found that the ratio varied between 1/2 and 1/5, and that a ratio >1/2 indicated a widened dural sac and <1/5 would be conclusive of stenosis (39). In 2003, Oosterhof et al. used this article as their reference for a ratio calculated from the proportion between the vertebral diameter and the dural sac diameter, the dural sac ratio, (DSR), measured on sagittal MR images. An increased DSR was used as a sign of DE (40). Since the publication of Oosterhof´s article several papers have used DSR as a feature of DE, including paper I and II in this thesis.

Most recent papers on DE have used either CT or MR imaging for assessment of this feature. However, conventional radiography has been published as a plausible method for detection of DE by some authors also the last years (41;42).

Myelography is another possible method to visualize DE. Myelography was introduced in the early nineteen forties, first with air (as a negative x-ray contrast medium) injected in the subarachnoid space, and later with positive contrast media, first with oil based contrast media, and later with water-soluble substances injected into the subarachnoid space. The oil based contrast media and ionic water-soluble contrast media were reported to give epileptic activity and adhesive arachnoiditis. Non-ionic iodine contrast medium was introduced in the early nineteen seventies, and this gave much less side effects (43). Myelography visualize the dural sac much better than does conventional radiography, which only shows a projection of the bony canal. Injection of contrast agents into the subarachnoid space, also non-ionic water-soluble substances, does however include a risk of complications.

Compared to conventional radiography, MRI and CT give considerably more information on the dural sac, and compared to myelography these methods in general include no contrast medium injection into the subarachnoid space. In 1983, Fishman et al. published an article where CT was performed in 5 MFS patients for examination of the lumbar spine and sacrum, and DE was found (44). Since then a number of articles about MFS have presented methods on how to assess DE by using conventional x-ray films, CT, and MR imaging, but no gold standard for the diagnosis of DE has emerged (40;45-52). Compared to CT, MRI is superior in depicting the soft tissues of the spinal canal, including the dural sac and dural sac herniations. Showing also bony scalloping, it may therefore be considered the best method in the diagnosis of DE.

4.5.3 Imaging of scoliosis

"Scoliosis > 20 degrees or spondylolisthesis" is one of the eight manifestations that may contribute to a major skeletal criterion in the Ghent 1 criteria. Scoliosis is an abnormal side-to-side curve of the spine with associated vertebral rotation, that affects as many as 4% of all adolescents (53). The scoliosis curve should optimally be imaged in a way that shows the effect of gravity on the curve's magnitude, i.e. with the patient erect. Also useful in assessing scoliosis in patients, are posteroanterior or anteroposterior side-to-side bending images (53). Spondylolisthesis is depicted with conventional radiography and CT, and may also be visible on MRI.

4.5.4 Imaging of the hips

Protrusio acetabuli (PA) was counted as a one of eight skeletal manifestations for MFS in the Ghent 1 nosology, and is assigned a systemic feature for the disease in Ghent 2. PA is found in quite a high proportion of MFS patients, varying in different studies based on study group and method of assessment. PA is an inward protrusion of the acetabulum as a rounded mass into the pelvis (54), and is seen in different disorders including primary idiopathic cases and secondary to neoplastic, infectious, metabolic, inflammatory, traumatic, congenital and genetic disorders (55).

Radiographic criteria for PA include the acetabular line abnormally positioned, a center-edge angle (CEA) of Wiberg of > 40° (Steel's method, CEA > 50°) (Fig. 1) and crossing of the "teardrop" by the ilioischial line (56;57). According to Armbuster et al., "the diagnosis of protrusio acetabuli is warranted if the acetabular line projects medial to the ilioischial line by 3 mm or more in men and by 6 mm or more in women (57) (Fig. 1).
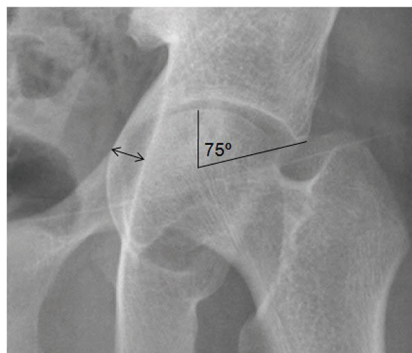
Figure 1. AP radiograph of left hip with protrusio acetabuli showing the acetabular line projecting medial to the ilioischial line by more than 6 mm (double arrow). The center-edge angle is 75°. Eighteen-year-old male patient.

Based on the various methods for assessing PA in conventional radiographs, authors have reported different prevalences of PA. Sponseller et al. (58) found that 16% of MFS patients had PA according to the Armbuster method (57), and 27% using Steel´s method (59). Yule et al. found a prevalence of 60% in their population of MFS patients using Kulman´s method for PA, which is a combination of an abnormally positioned acetabular line and either the center-edge angle of Wiberg ≥ 40 degrees, or crossing of the teardrop by the ilioischial line (60).

PA has mostly been examined by conventional radiography, and the varying results in different studies illustrate the problems with this method. In the article "A new tilt on pelvic radiographs: a pilot study", Richards et al. discuss how the different methods will give different results depending on the degree of pelvic tilt (61).

MRI has been advocated as a modality for examining PA in an article by Chen et al. (62), and their method for assessment of PA is further studied in our article "CT of the hips in the investigation of protrusio acetabuli in Marfan syndrome. A case control study" (paper III). Both MR and CT can give detailed sectional images of the hips, and direct depiction of acetabular protrusion is not hampered by changes in pelvic tilt. CT is superior to MR in visualizing cortical bone, and although not free of ionizing radiation, high-quality CT of bony structures may be performed with low radiation doses.

4.5.5 Imaging of the thoracic cage and lungs

Emphysematous air filled expansions or blebs have been found in MFS patients, and are counted as features of the disease in the Ghent 1 nosology (Fig. 2). In the revised criteria for MFS from 2010 (Ghent 2), sole emphysematous blebs in the lungs do not count as features of MFS, but spontaneous pneumothorax is still reckoned a sign of MFS. Large blebs, especially in the apical part of the lungs can cause spontaneous pneumothorax. Abnormalities of the thoracic cage such as pectus excavatum and/or carinatum are also present in many MFS patients, and are features for MFS in Ghent 1 and 2 (Fig. 3).

Conventional radiography of the chest has been used to examine the heart, lungs and thoracic cage for more than 100 years, and is still the most commonly used method for chest imaging. CT gives, however, a much more detailed picture of the thoracic cage, and different methods of CT (for instance CT angiography, CTA, or high resolution CT, HRCT) are used for different indications.

HRCT is a special application of computed tomography where imaging parameters are chosen to maximize spatial resolution, and this method is excellent for evaluation of the lung parenchyma. HRCT scanning is a valuable device allowing identification of the presence, extent and severity of interstitial lung disease (63). A narrow slice width (usually 1–2 mm) is used together with high spatial resolution image reconstruction algorithm. In addition, the field of view is minimized to make each pixel small.
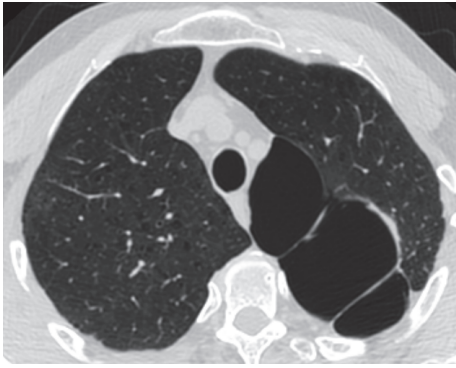
Figure 2. HRCT of MFS patient with emphysematous blebs in the left lung, and centrilobular emphysema in especially the right lung.

Figure 3. HRCT of MFS patient with pectus excavatum and aortic valve replacement.

5. Aims of the study

General aims were:

To explore the prevalence of different manifestations of Marfan syndrome by using radiological methods in the investigation of this disease. To evaluate different imaging methods in each organ system examined by radiological methods.

Specific aims were:

1. To explore the phenotype, the prevalence of each 'major criterion' and 'organ involvement' through a prospective and complete investigation of all features of the Ghent 1 criteria in an adult group of patients with a proven diagnosis of MFS (paper I).
2. To establish the prevalence of dural ectasia (DE) in an adult population fulfilling the Ghent 1 criteria for MFS, and to assess definitions of DE by MR or CT examinations (paper II).
3. To establish the prevalence of protrusio acetabuli (PA) in adults fulfilling the Ghent 1 criteria for MFS by using CT examinations (paper III).
4. To establish the prevalence of pulmonary artery dilatation in MFS by MRI or CT, to correlate diameter of the vessel with aortic disease, and explore predictors of pulmonary artery dilatation in MFS (paper IV).

6. Materials and methods

6.1 Study population

The "Norwegian Marfan study" was a cross-sectional study of adults with presumed MFS living in Norway. The study patients were recruited either by an advertisement requesting adult MFS patients to participate (Journal of the Norwegian association for MFS and MFS-like disorders), by a letter sent to adults (> 18 years) registered as having MFS in a national database of MFS patients (National Resource Center for Rare Disorders, Sunnaas Rehabilitation Hospital), or through an invitation to patients suspected of having MFS, distributed by the Department of Thoracic and Cardiovascular Surgery, Rikshospitalet, Oslo University Hospital.

One hundred and nine patients gave informed consent to participate, but only 105 attended the whole study. The 105 patients consisted of 67 women aged 20–69 years, mean 41.2 (SD 13.6)

years, and 38 men aged 19–62 years, mean 35.1 (SD 11.3) years. Of the 105 study patients 90 had been given the diagnosis of MFS previously, and 15 were suspected of having MFS.

The present substudy "Radiological Imaging in the Investigation of Marfan Syndrome" also comprises two control populations. In our assessment of dural ectasia (paper II), control subjects were chosen from the pool of patients in the radiologic archive (PACS) of the Department of radiology, Oslo university hospital, on the basis of the following criteria: sex- and age-matched asymptomatic persons with respect to the lumbosacral spine and without any known connective tissue disease or compression fractures, screened with MR imaging for malignancy in the lumbosacral spine, but with no evidence of malignant disease in this area. The controls included 101 subjects, 64 women aged 18-65 years, mean 39.6 (SD 12.9) years and 37 men aged 18–70 years, mean 35.7 (SD 12.3) years.

In our investigation of acetabular protrusion in MFS (paper III), the control cases were also chosen from the radiological archive (PACS) of the Department of radiology, Oslo university hospital, based on the following criteria: sex- and age-matched asymptomatic persons with respect to the hips and without any known connective tissue disorder, examined by CT of the abdominal and/or pelvic area due to symptoms from the abdominal area or with suspected vessel disease in the pelvic or abdominal region. Patients with liver or kidney transplants were excluded. The controls included 107 subjects, 68 women aged 19-69 years, mean 40.9 (SD 13.7) years, and 39 men aged 19-64 years, mean 35.8 (SD 12.1) years.

6.2 Radiological examinations

MRI of the thoracic aorta, the pulmonary artery, and the lumbosacral column was performed in one session unless contraindicated, when CT examinations were obtained instead.
CT was used for tomographic imaging of the thoracic cage and the hip joints, and for projection imaging of the vertebral column (scout view).

MRI of the thoracic aorta and the pulmonary artery was performed using a 1.5 T unit (Signa LX, GE Healthcare, Milwaukee, Wisconsin) in axial and oblique sagittal planes using a standard ECG-gated T1-weighted SE sequence without intravenous contrast medium injection. Repetition time equalled the R–R interval, echo time was minimum 9.32 ms to maximum 39.976 ms, slice thickness was 7 mm in the axial plane, and 4 mm in the oblique sagittal plane.

CT of the thoracic aorta and the pulmonary artery was obtained on a ProSpeed SX scanner (GE Healthcare, Milwaukee, Wisconsin) with 5 mm slice thickness in patients in whom MRI was contraindicated.

HRCT of the lungs was performed on a ProSpeed SX scanner (GE Healthcare, Milwaukee, Wisconsin) with 1 mm slice thickness and 10 mm distance between slices.

MR imaging of the lumbosacral spine in the study group was performed using a 1.5 T unit (Signa LX, GE Healthcare, Milwaukee, Wisconsin). T1-weighted (TR/TE = 375/9 ms) and T2-weighted (TR/TE = 3500/120 ms) turbo spin-echo sequences were obtained in the sagittal plane with 4 mm section thickness. The T2-weighted sequence was repeated in the coronal plane and in 5 angulated axial planes parallel to the 5 lumbar intervertebral disks.

MR imaging of the lumbosacral spine in the control patients was performed with a 1.5 T unit (Signa, GE Healthcare, Milwaukee, Wisconsin) with sagittal and coronal T1-weighted fast spin-echo sequences (TR/TE = 500/9–13 ms) and sagittal and coronal short-inversion-time inversion recovery sequences (TR/TI/TE = 4300/150/34 ms). Section thickness and interslice gap were 4 and 0.5 mm for sagittal images and 7 and 1 mm for coronal images, respectively.

CT imaging of the hips in the study patients was performed by a ProSpeed SX scanner (GE Healthcare, Milwaukee, Wisconsin) with 3 mm slice thickness.

CT imaging of the hips in the control patients was performed on different scanners with slice thickness 3 mm or less.

6.3 Statistical approach

All statistical analyses were performed by SPSS versions 13-18 (SPSS, Chicago, Il). Significance level was set to 5%. Continuous data were described as mean and standard deviation or median and range for normally distributed or skewed data, respectively. Categorical data were described as frequency and percentage.

Univariate statistical analyses on differences between groups were analyzed with independent sample t-test or chi-square, as appropriate, and correlation assessed with Pearson correlation

coefficient. Skewed data were analyzed with a non-parametric Kruskal-Wallis test. For continuous data, difference in mean between the study groups was analyzed with one-way ANOVA, and for multiple comparisons Tukey or Bonferroni post hoc test was done. Pearson's chi-square test was used for categorical data. Odds ratios were calculated for nerve root sleeve herniations. Multivariate analysis on factors influencing pulmonary artery diameter was done with a multiple linear model. Statistical analysis of dural sac diameter between the groups was adjusted for sex and age using a general linear model.

7. Summary of papers

7.1 Paper I. Prevalence data on all Ghent features in a cross-sectional study of 87 adults with proven MFS.

In order to investigate the phenotype, i.e. to explore the prevalence of each "major criterion" and "organ involvement" in an adult cohort with proven Marfan syndrome, we investigated 105 adults with suspected MFS for all the features of the Ghent 1 criteria. Eighty seven (83%) fulfilled the different features through 56 different combinations of the major criteria and organ involvement.
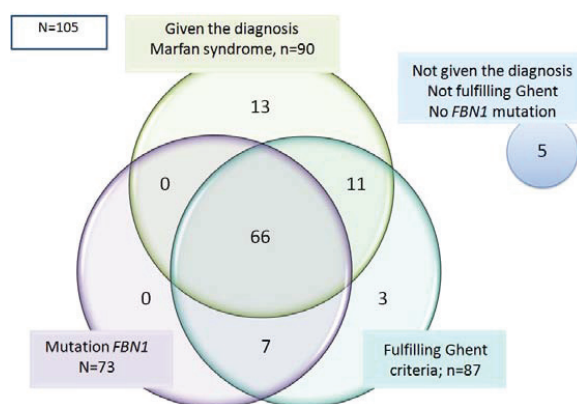
Using the full version of the Ghent 1 criteria on 105 individuals refuted the MFS diagnosis in 13 out of 90 patients who had been diagnosed earlier, and verified the diagnosis in 10 of 15 persons with suspected MFS. Figure 4 gives an overview of the diagnostic results.

Figure 4. Diagnostic results for entire study group (n=105). Reproduced with permission from Svend Rand-Hendriksen (2).

The major dural criterion (DE) was fulfilled in 91% of the Ghent positive cohort, a major genetic criterion (positive family history and/or *FBN1* mutation) was found in 89%, a major ocular criterion in 62%, and a major cardiovascular criterion in 53% of the MFS patients. The

major skeletal criterion was fulfilled in 38% of the Ghent positives. As much as 16% (14 persons) of the Ghent positive cohort were dependent of DE to fulfill the diagnosis of MFS.

In spite of the great diversity of combinations to fulfill the diagnosis according to the Ghent nosology, a combination of the dural major criterion and the presence of genetic major criteria could identify 69 (79%) out of 87 affected individuals with MFS in our cohort. This indicates an early investigation of those systems when suspicion of MFS has been raised in adults.

7.2 Paper II. Dural ectasia in Marfan syndrome. A case control study.

In order to investigate the prevalence of dural ectasia in a cohort of patients fulfilling the Ghent criteria for MFS, and to find the best criteria for assessment of dural ectasia, we studied the lumbosacral spine of 105 adults suspected of having MFS with MR imaging at 1.5 T (unless contraindicated, when CT was obtained instead). One-hundred and one sex and age-matched persons screened for malignancy by MR imaging constituted the control group.

Dural ectasia (DE) is one of the major criteria of MFS in the Ghent 1 nosology and has been defined as "enlargement of the neural canal anywhere along the spinal column, but nearly always in the lower lumbar and sacral regions; thinning of the cortex of the pedicles and laminae of the vertebrae; widening of the neural foramina; or an anterior meningocele". A number of articles about MFS have presented methods on how to assess DE by using conventional x-ray films, CT, and MR imaging, but no gold standard for the diagnosis of DE has emerged.

We measured lumbosacral anteroposterior vertebral body diameters (VBD) and dural sac diameters (DSD). Dural sac ratios (DSR = DSD/VBD) at levels L3 through S1 were calculated. Anterior meningoceles, herniations of nerve root sleeves, and scalloping were characterized.

Three patient groups were identified: 1) fulfilling Ghent criteria independent of DE (n = 73), 2) fulfilling Ghent criteria dependent on DE (n = 14), and 3) suspected MFS, not fulfilling Ghent criteria (n = 18). The control and study populations were compared in aggregate, and consensus readings in addition to interobserver agreement were studied.

We found that:

1) Anterior meningoceles were present in Ghent-positive patients only.

2) Herniations of the nerve root sleeves were frequently present in Ghent-positive patients, in 73% of group 1 (MFS independent of DE), and in 71% of the patients in group 2 (MFS dependent on DE). Only one person (1%) of the controls had herniation of a nerve root sleeve.

3) DSD sacrum > DSD L4 was found in 52% of group 1, and in 29% of group 2. Five percent of the controls had this finding.

4) DSR S1 > 0.59 was present in 59% of group 1, and in 85% of group 2, while 7% of the controls had this feature.

On the basis of the ROC analysis, a cut-off value of 0.59 for DSR at level S1 was suggested, giving a sensitivity of 70.5% and a specificity of 92.7% as a marker for MFS. A total of 86% of our Ghent-positive patients independent of DE fulfilled the combined signs of DE described above.

We concluded that the above mentioned features (1-4) for DE should be the basis for the diagnosis of DE. MR imaging of the spine is encouraged to identify DE and thus strengthen a potential diagnosis of MFS.

7.3 Paper III. CT of the hips in the investigation of protrusio acetabuli in Marfan syndrome. A case control study.

In order to establish the prevalence of protrusio acetabuli (PA) in adult persons fulfilling the Ghent 1 criteria for MFS, and to find the best criteria for the assessment of PA, we studied CT of the hips in 105 adults with suspected MFS, and 107 sex- and age-matched controls. Asymptomatic persons with respect to the hips, and without any known connective tissue disorder, examined by CT of the abdominal and/or pelvic area chosen from the radiological archive in our department, constituted the control group. Eighty-seven of the 105 persons suspected of having MFS fulfilled the Ghent 1 criteria (= Ghent positive).

PA is an inward protrusion of the acetabulum as a rounded mass into the pelvis, and varies from a few millimeters to five centimeters, and is seen in different disorders including primary idiopathic cases or secondary to neoplastic, infectious, metabolic, inflammatory, traumatic, congenital and genetic disorders.

PA is one of the eight manifestations that may contribute to the major skeletal criterion for Marfan syndrome (MFS) according to the Ghent 1 nosology, and is included as one of the features of the "systemic score" in the newly revised Ghent 2 criteria. Diagnosing PA has been a point of discussion since the accuracy of measurements on conventional pelvic radiographs is uncertain and may vary with pelvic tilt. Few authors have assessed the different radiological methods in a validated way, and the definition of PA has varied depending on the radiological method.

A qualitative assessment of PA was performed. A new method for estimating the degree of PA was introduced with measurement of the parameter CWD (circle-wall distance), where a circle with 10 cm radius was fitted to the inner pelvic wall at the level of the acetabulum. PA was diagnosed qualitatively in 74.7% of Ghent positive persons, in 27.8% of Ghent negative persons (the 18 persons suspected of MFS without fulfilling the Ghent 1 criteria), and in 3.7% of the controls. PA was bilateral in 81.5% of Ghent positive persons, and in 50% of controls. CWD was significantly different between the three groups ($p<0.001$). ROC analysis of CWD vs. qualitative diagnosis of PA showed an area under the curve of 0.99 (95% CI 0.98–1.0); a CWD cut-off value of 1.25 mm resulted in a sensitivity and specificity for PA of 95.5% and 97.6%, respectively. Interobserver agreement for assessing PA qualitatively was high with a kappa value (κ) of 0.88 (95% CI 0.81–0.95) for the right hip and 0.92 (CI 0.81–1.0) for the left hip. The circle method had an interclass correlation coefficient (ICC) of 0.91 (95% CI 0.89–0.95) and 0.89 (95% CI 0.81–0.93) on the right and left side, respectively.

We concluded that PA was found significantly more often in MFS persons than in controls. Both our CWD and qualitative method was found to be robust and highly reproducible, giving a direct assessment of pelvic protrusion irrespective of pelvic shape or tilt.

7.4 Paper IV. The pulmonary artery in Marfan syndrome patients. A cross-sectional study.

In order to establish the prevalence of pulmonary artery dilatation in Marfan syndrome (MFS) by radiological methods, to correlate diameter of the vessel with aortic disease, and explore predictors of pulmonary artery dilatation in MFS, we performed MR or CT imaging of the pulmonary artery and aorta in 87 patients with proven MFS. According to the Ghent 1 nosology "dilatation of the main pulmonary artery, in the absence of valvular or peripheral

pulmonary stenosis or any other obvious cause, below the age of 40 years", is considered a minor cardiovascular criterion of MFS.

Axial diameters of the pulmonary artery root and trunk were measured perpendicular to the long axis of the vessel on axial images. Aortic root diameters were measured on oblique sagittal images perpendicular to the long axis of the vessel. Measurements were compared to normal values based on MR and CT in the literature.

MR and CT measurements of the pulmonary artery showed mean (SD) diameters of the pulmonary artery root and trunk of 35.0 (4.6) mm and 29.8 (3.8) mm, respectively. According to Ghent 1 criteria for pulmonary artery dilatation, which are based on nomograms of the aortic root, 7 out of 39 patients (17.9%) under 40 years of age had dilated pulmonary artery root, while none had dilatation of the pulmonary artery trunk. Compared to published normal values for adult pulmonary artery trunk diameters, 47 (54%) of the 87 patients had dilated pulmonary artery trunk, i.e. ≥ 30 mm.

Thirty (34.5 %) of the 87 Ghent positive patients had previous surgery on the ascending aorta. The remaining 57 MFS patients without previous aortic surgery had echocardiographic measurements indicating that 16 had dilated aortic root according to the Ghent 1 criteria (nomograms by Roman et al.). However, when the aortic root diameters were reassessed with MR or CT, 40 of these 57 patients had dilated aortic roots according to the same criteria. Thus, based on MR or CT a total of 70 (80.5%) patients fulfilled the major cardiovascular criterion for MFS, i.e. had an operated or dilated ascending aorta.

Pulmonary artery root and trunk diameters were significantly larger in patients with previous surgery on the ascending aorta compared to those without such surgery (p=0.041 and p=0.027, respectively). Pulmonary artery trunk diameters were significantly larger in patients with ascending aortic disease (dilatation or previous surgery) than in those without (p=0.018), but the pulmonary artery root diameters were not significantly larger in this patient group (p=0.104). A multivariate analysis suggested that previous surgery on the ascending aorta was a significant predictor of pulmonary artery trunk dilatation, but not of pulmonary artery root dilatation.

Seven (14.9%) of the 47 patients with dilated pulmonary artery trunk diameter ($\geq$ 30 mm) had normal diameter of the aortic root, while 20 (42.6%) had a dilated native aortic root, and 20 (42.6%) had previous surgery on the ascending aorta.

We concluded that pulmonary artery dilatation is a common finding in MFS (54%), and should be assessed using cut-off values based on pulmonary artery diameter measurements in the normal population. MR or CT imaging seems to provide more reliable results for pulmonary artery dimensions than echocardiography. Severe disease of the ascending aorta is a significant predictor of pulmonary artery trunk dilatation in MFS patients, but such dilatation may occur even in the absence of visible aortic disease.

8. Discussion

8.1 Study and control populations

The Norwegian Marfan study intended to be a cross-sectional study of the adult Norwegian MFS population. All criteria for the syndrome were examined according to the Ghent 1 criteria. One hundred and five persons were included, and 87 of these fulfilled the Ghent 1 criteria for MFS. Through the invitation letters sent to patients with proposed MFS, and through the advertisement in the Journal of the Norwegian association of MFS and MFS-like disorders, we believe that the majority of the genuine patient group was informed. Despite the fact that MFS affects men and women equally often, there was a skewed gender representation in our study, 64% of the participants being women. This might be accidental, but could also reflect a gender difference in the willingness to participate in studies. In addition, the men as a group were younger than the women, and these facts together may constitute a bias selection.

Control patients were included in our assessment of dural ectasia and acetabular protrusion in MFS. The prevalence of dural ectasia in the general population was not known, and previous case control studies addressing this topic were few and had control groups that (with one exception) tended to be small. The control groups had furthermore not been sex- or age-matched, and they included patients with low back symptoms (40;45;47-49). Our control group for DE included 101 sex- and age-matched controls without low back symptoms, giving us reason to assume that our findings in that group would be representative for a

normal population. Our results indicate that DE is a common finding in MFS, but present in only a few percent of healthy persons without back pain.

Our main reason for including controls in our examination of acetabular protrusion was lack of knowledge concerning the prevalence and degree of protrusion in the normal population when assessed with CT. No previous studies on this topic were found. To avoid radiation exposure to healthy persons by CT, no healthy volunteers were included; all 107 sex- and age-matched controls were chosen from the radiological archive of our hospital.

8.2 Radiological methods

In our investigation of the study population we intended to use radiological methods described by the Ghent 1 article published in 1996 (1). However, we did a pilot study of 23 patients with suspected MFS, 18 fulfilled the Ghent 1 criteria for MFS, and based on this pilot study it was decided that some radiological examinations could be exchanged with more modern methods. For examination of the hips for protrusio acetabuli radiography was exchanged with CT because the latter method gives much more detailed information of the acetabular shape than does conventional radiography. MR imaging of the vertebral column in the investigation of DE was chosen instead of CT or radiography because this method depicts soft tissue as the dural sac, better than does CT or radiography, and in addition it does not include ionizing radiation. CT of the thoracic cage depicts blebs in the lungs far better than radiography. To optimize examination of the ascending aorta, MR imaging was chosen in addition to echocardiography.

The examinations in our study were performed in the period of 2003-2005, and since then MR and CT techniques have improved substantially. To reduce possible side-effects to a minimum, contrast-enhanced imaging was not included, resulting in less than optimum imaging of the aorta and pulmonary artery. Today, non-enhanced 3D MRI using a balanced gradient echo sequence with ECG and respiratory gating would have been used for imaging of the great thoracic vessels, but although our ECG-triggered 2D TSE sequences are far from today's state of the art, they are still adequate for diameter measurements.

8.3 Prevalence data on all Ghent features (paper I)

In this cross-sectional study of 105 adults suspected of having MFS, all patients were examined by the same group of investigators with standardized and complete assessment of all features in the Ghent 1 criteria. Eighty-seven patients fulfilled the criteria in as much as 56 different combinations of criteria and involvement. That confirms the need for the complete Ghent criteria to be identified in studying MFS, although the majority of them could have been identified by combined assessment of dura and the family history, supplemented with DNA analysis in family-negative cases.

Dural ectasia was found in 91% of the MFS patients, and DE was the sign most prevalent of all the Ghent criteria, followed by the major genetic criterion (89%), and ectopic lenses (62%). We based our diagnostic criteria for DE on a combination of findings from our own case control study of DE and proposed signs of DE from the literature. In addition to qualitative signs for DE and DSD sacrum > DSD L4, cut-off values of DSR at level L5 and S1 according to Oosterhof et al. (40) were used as diagnostic criteria for DE. However, Oosterhof et al. proposed a combination of elevated DSR at level L3 and S1 as a specific indicator to identify MFS (40). In our study, DSR at level L3 had no discriminating value for the presence of MFS because we found no significant differences between Ghent-positive patients independent of DE and the controls.

The prevalence of DE in our study was among the highest found in the literature, but it was comparable to studies by Oosterhof et al. (95%) and Fattori et al. (92%) (40;49). Pyeritz et al. found a lower prevalence of DE (63%) in 1988 (46), and Radonic et al. found DE in 76% of their patients in an article published in 2011 (22). As much as 16% (14 persons) of the Ghent positive patients were dependent of DE to fulfill the diagnosis of MFS. This underscores the importance of investigating this feature of MFS. In the Ghent 2 criteria DE is given less significance than in the Ghent 1 nosology. In a newly published study by Radonic et al. (22) 180 Ghent 1 positive patients were tested for the Ghent 2 nosology; three patients with dilated ascending aorta according to the new z-score system used by the Ghent 2 nosology, had their diagnosis of MFS rejected because of low systemic score according to Ghent 2. None of these three were found to have any other connective tissue diseases. These patients fulfilled Ghent 1 based on two major criteria, dilatation of the aortic root and DE in addition to involvement of another system. Because of the reduced significance of DE in Ghent 2, the criteria for MFS were not fulfilled.

Protrusio acetabuli (PA) is regularly found in MFS patients*,* and CT of the hips was chosen instead of conventional radiography, partly because previous studies had given varying results dependent on method for assessment of PA by conventional radiography, and also because CT is a superior method to depict bony structures. We used an ellipse to assist us in the qualitative evaluation PA, and defined PA as present when the bottom of the acetabulum protruded into the ellipse. We found protrusio acetabuli in 52 (59.8%) of the 87 MFS patients. Our evaluation of the radiological findings was later refined, leading to an even higher prevalence of PA in our MFS patients, 74.7% (paper III).

HRCT was chosen to study *blebs in the lungs*, a criterion of the Ghent 1 nosology. We found apical blebs in 16 out of 87 MFS patients. In a study by Wood et al. in 1984, only 5 out of hundred MFS patients had apical blebs based on conventional radiography examinations (64). Our findings probably reflect the much higher sensitivity of HRCT compared with conventional radiography in detecting changes in the lung parenchyma. In addition to blebs in the lungs the HRCT study made it possible to depict *pectus excavatum* and *carinatum*. Pectus carinatum was found in 57 (65.5%) of our MFS patients.

We assessed *scoliosis* based on scout views from the CT examinations performed. Additional conventional radiography in the erect position would have been a better method to study scoliosis, but emphasis was put on minimizing radiation to the patient. Scoliosis and/or spondylolisthesis were found in 26.4% of the MFS patients.

The ascending aorta was measured by echocardiography and MRI in our study, but in paper I results were based on echocardiography only, in accordance with the Ghent 1 nosology (1;65). The prevalence of ascending aortic disease (major cardiovascular criterion) was 53%, and that of mitral valve prolapse 14% in our study, and was among the lowest reported in individuals fulfilling the Ghent 1 criteria. As most studies that were found in the literature emerged from specialized 4th level cardiovascular centres serving individuals with severe aortic or cardiovascular disease, patient selection may explain the high prevalence of cardiovascular pathology in other reports. In the hindsight's light, another explanation of why the number of patients with affected ascending aorta was relatively low, could be that our echocardiographic measurements underestimated aortic diameters. There was a large discrepancy between the echocardiographic and the MR/CT results on diameter of the

ascending aorta, where MR/CT gave a much higher prevalence of ascending aorta disease (paper IV).

According to the Ghent 1 criteria none of our MFS patients had dilated pulmonary artery. In the discussion of paper I we wrote: "Using Nollen's upper limit of normality for the pulmonary artery trunk, 34.8 mm, 13 out of 87 persons fulfilling Ghent had enlarged pulmonary trunk (median diameter 30 mm; range 23–38 mm)". The problem with this statement is that the wrong cut-off value, the cut-off value for the pulmonary artery root instead of the trunk, was used. The cut-off value proposed by Nollen et al. for the trunk was 28 mm, which would have given a much higher prevalence of dilatation of the pulmonary artery (66). Also De Backer et al. used Nollen´s cut-off values wrong in their article on minor cardiovascular signs in MFS (67). So there has been a general confusion in the literature on the pulmonary artery in MFS patients. MRI with modern sequences should be used for assessment of the pulmonary artery trunk diameter, and pulmonary artery cut-off values must be used instead of aortic cut-off values.

8.4 Dural ectasia (paper II)

Dural ectasia is found in a high percentage of MFS patients, and was according to the Ghent 1 nosology a major criterion for this disease. A proportion of the MFS patients are dependent of DE to fulfill the diagnostic criteria for MFS. In our study 14 (16%) out of the 87 MSF patients were dependent on the finding of DE to get the diagnosis. This was in line with the result in a study by Sznajder et al., 2010 (42) where 10% of their MFS patients were dependent of DE to fulfill the criteria for MFS. This strengthens the proposal that the lumbosacral spine should be imaged when MFS is suspected.

We divided the study patients in three groups: (1) fulfilling Ghent 1 independent of DE, (2) fulfilling Ghent 1 dependent of DE, and (3) not fulfilling Ghent 1. By adding a large control group, the prevalence of DE in the healthy population could also be assessed.

Assessment of DE in our study included qualitative and quantitative signs. Qualitative signs were anterior meningoceles (i.e. spinal fluid collection covered by dura inside the pelvic cavity) or herniation of dura along the nerve root sleeves. Quantitative signs included DSD sacrum > DSD L4 suggested by Ahn et al. (51), and cut-off values for DSR at level L5 and S1 suggested by Oosterhof et al. (40). Oosterhof et al. found that a combination of DSR at level

L3 and DSR at level S1 had a high diagnostic sensitivity and specificity for MFS (40). As a marker of MFS, DSR at level S1 had the highest sensitivity and specificity in our study. DSR at level L5 gave the second best results. No significant differences at level L3 between DSR of Ghent positive patients independent of dura and controls were found. By including qualitative findings, and replacing the cut-off values for DSR proposed by Oosterhof et al. at level L5 and S1 by a cut-off value at level S1 of 0.59, the prevalence of DE was found to be 86% in group 1 (MFS patients not dependent on DE for their diagnosis), and 9% in the controls. Söylen et al. found in their case control study of MFS patients that according to the method of Oosterhof et al. 88% of MFS patients and 47% of controls had dural ectasia (40;68).

Some recent reports about DE in MFS have postulated that quantitative signs of DE have major advantages over qualitative assessments because cut-off values can be used more uniformly than qualitative signs (40;48). We found qualitative signs as nerve root sleeve herniation and anterior meningocele very useful because they are highly specific for DE. Ten of our patients would not have been assigned the major criterion DE if nerve root sleeve herniation had not been a sign of that feature. The presence of nerve root sleeve herniation at at least one vertebral level had a sensitivity of 72.6% (95% confidence interval [CI], 67.6%–77.6%) and a specificity of 99.0% (95% CI, 95.4%–99.8%) in diagnosing MFS.

Although the dural sac is a soft-tissue structure, DE has been defined to include bony changes of the spine, such as thinning of the cortex of the posterior vertebral elements, widening of the neural foramina, and vertebral scalloping in addition to the presence of a patulous dural sac and anterior meningoceles (1;69). MR imaging, like CT and conventional radiographs, identifies the secondary osseous changes associated with DE, but MR imaging also allows the direct visualization of the soft tissues of the entire spine. In the ongoing discussion on which methods are necessary to depict DE, Sznajder et al. have recently suggested that conventional radiography should be used as first line screening for suspected MFS patients, and that CT or MRI should be reserved for unresolved cases (42). Conventional radiography was found to have a low sensitivity (35.3%), but very high specificity (100%), indicating that the majority of DE cases would remain undetected using radiography alone (42).

The Ghent 2 nosology regards DE as a sensitive but unspecific sign of MFS (8). It is argued that no preferred methods (CT or MRI) or uniformly accepted cut-off values for DE have

emerged from the literature. In our study using MR imaging, we compared MFS patients independent of DE to controls, and found that the presence of nerve root sleeve herniation at one or more levels had high specificity for MFS compared to controls. In line with this, DE was not identified as an incidental finding in a study concerning MR imaging of the lumbar spine in persons without back pain (70). On the basis of our ROC analysis, a cut-off value of 0.59 for dural sac ratio at level S1 was suggested, giving a sensitivity of 70.5% and a specificity of 92.7% as a marker for MFS.

We recognize that DE is found in other connective tissue diseases, such as neurofibromatosis 1, Ehlers-Danlos syndrome and Loeys-Dietz syndrome, and it may be argued that DE is a sign of inherited connective tissue disorders. Based on our study we believe that DE is sensitive and specific for connective tissue diseases, including MFS. It is a well documented sign for these diseases, and its detection should be given preference in the diagnostic process of MFS.

8.5 Protrusio acetabuli (paper III)

Protrusio acetabuli (PA) is regularly described in MFS patients, but we found only one study based on MR examinations (62) in the literature, and none based on CT. Radiography of the hips on this indication is described in many papers (55;58-60;71). The reported prevalence of PA in MFS based on conventional radiography has varied in different studies (56). Sponseller et al. studied PA in children and adults with MFS and found different percentages of PA depending on the method of assessment; Steel´s method (59) gave 27% of the patients the diagnosis of PA, while the method by Armbuster (57) gave 16% (58).

A newly published study by Richards et al. concludes that as pelvic tilt increases, classic radiographic measurements of PA become unreliable (61). The authors found too much variation in the results to recommend any standard radiographic test. They claim that despite a variety of radiological measurements, few authors have assessed the different methods of radiological analysis in a validated way.

In our case control study CT was chosen due to its direct visualization of the acetabular shape and its superior depiction of cortical bone. Qualitative assessment of PA in our study was defined as any degree of intrapelvic protrusion of the medial pelvic wall at the level of the acetabulum. Using this criterion, we found a very high percentage of PA in our MFS persons (74.7%) as compared to the controls (3.7%). The finding of PA in 27.8% of the persons

suspected of having MFS but not fulfilling the Ghent criteria probably reflects that several of these persons had other connective tissue diseases that might predispose for PA. For quantification of PA we introduced a circle with 10 cm radius and measurement of the circle-wall distance (CWD). The circle was fitted to the inner pelvic wall at the level of the acetabulum, and CWD was measured as the distance from the circle to the most medial point of the inner acetabular wall. Measurement of CWD was easily performed with a high interobserver reproducibility. ROC analysis of CWD vs. qualitative diagnosis of PA showed an area under the curve of 0.99 (95% CI 0.98–1.0); a CWD cut-off value of 1.25 mm resulted in a sensitivity and specificity for PA of 95.5% and 97.6%, respectively. ROC analysis of CWD in differentiating MFS patients from controls showed a sensitivity and specificity in diagnosing MFS of 68.8% and 97.2%, respectively, when using a CWD cut-off value of 1.25 mm. Measurement of CWD appears to be a useful method in estimating the degree of PA, but the simplest way to determine whether PA is present is to evaluate the shape of the inner acetabular wall at CT (or MRI); any inward protrusion should be termed PA.

In our assessment of PA, we also evaluated an MRI-based method published by Chen et al. (62). Measurement of acetabular protrusion according to Chen et al. was possible in 68.9% of all study persons and controls. Chen's method requires that the ischial spine is depicted in the same axial image as the medial most point of the acetabular fossa, and this was often not the case. When the method could be used, it had a high interobserver reproducibility, but a low accuracy in detecting PA. No statistically significant differences were found between controls, Ghent positive patients, and Ghent negative persons suspected of having MFS.

Our study indicates that CT is a reliable method that should replace conventional radiography in the diagnosis of PA. CT of the hips may be performed with low radiation dosage, but if radiation dosage is a concern (young patients, repeated examinations), MRI may be performed instead, most likely with the same accuracy as CT.

8.6 Pulmonary artery (paper IV)

Our study showed that when compared to normal values in healthy adult persons (72), more than half (54%) of our adult patients with proven MFS had dilatation of the pulmonary artery trunk, some (approx. 15%) even in the absence of dilatation of the aortic root or ascending aorta.

The Ghent 1 criteria of 1996 (1;72) included dilatation of the pulmonary artery as a sign (minor vascular criterion) of MFS, but in the revised criteria (Ghent 2) published in 2010 (8), this criterion was omitted. Reasons given were that pulmonary artery dilatation is not specific to the diagnosis of MFS, that complications of pulmonary artery disease are rarely seen, and that further research is needed regarding thresholds and the diagnostic utility of this finding (8). The uncertainty regarding threshold values for pulmonary artery dilatation is partly caused by the vagueness of the Ghent 1 criteria with respect to the pulmonary artery. The authors state that "until normal values for pulmonary artery diameter are available, dilatation can be detected provisionally by echocardiography, CT or MRI using nomograms for the aorta" (1). Furthermore, the Ghent 1 criteria do not specify which part of the pulmonary artery should be measured, the root or the trunk. In search for literature on the pulmonary artery diameter we found that most papers addressing upper normal values for the pulmonary artery have considered the pulmonary artery trunk only, and among those performed with axial imaging (66;72-75), only three have included an adequate number of subjects (72;74;75). The 126 subjects studied by Bozlar et al. (72) were imaged with nearly the same slice thickness as our MFS patients, and the age distribution was furthermore similar, 30.6 ± 7.9 years and 35.1 ± 11 years, respectively. Pulmonary hypertension and thoracic pathology had been excluded. We therefore consider this group of healthy adults as an adequate control group for our study.

In our study "Prevalence data on all Ghent features in a cross-sectional study of 87 adults with proven Marfan syndrome" (paper I) we found no MFS patients with dilated pulmonary artery based on the Ghent 1 criteria. The large discrepancy between the findings of pulmonary artery dilatation using nomograms for the aorta as recommended by Ghent 1 (1) and when using cut-off values based on 2 SD above the mean value in healthy volunteers, suggests that nomograms for the aorta are not suited for assessment of pulmonary artery dilatation.

Our preliminary measurements of native (not operated) aortic root diameters were performed with echocardiography and resulted in 16 out of 57 MFS patients having dilated aortic root. When remeasured with MR or CT, the number increased to 40 of 57. All aortic diameter measurements (echocardiography, MR, CT) were plotted into a nomogram based on echocardiographic measurements and included in the Ghent 1 criteria (1;65). The unusually low prevalence of aortic root dilatation when measured with transthoracic echocardiography, suggests that aortic root diameters were underestimated using this method. Echocardiographic measurement of the aortic root is commonly performed using a parasternal long-axis view of

the aortic root and measuring from "leading edge to leading edge", i.e. including the anterior wall but not the posterior wall in the diameter measurement. The acoustic window is restricted, and the maximum diameter of the vessel may not be included in the scan plane. Aortic aneurysms are defined by their maximum outer diameter, and assessment of aortic diameters with MRI or CT therefore usually includes the vessel wall on both sides of the lumen. In addition, axial MRI and CT may overestimate vessel diameter due to obliquity of the vessel with respect to the axial plane. Such overestimation will increase with increasing slice thickness due to partial volume effects. A source of error is also the pulsatile variation in aortic diameter from diastole to systole. With the multislice ECG-triggered MR technique used in our study, the different slices will be imaged at different time points throughout the cardiac cycle. The above mentioned factors may all have contributed to the discrepancies between echocardiographic and MRI/CT measurements. The major differences in imaging techniques also underscores the importance of using nomograms based on the same imaging modality as the one used for measurements.

The Ghent 2 criteria suggest that a recent ECG-gated 64 channel MDCT study by Lin et al. (34) should be used as reference material for CT examinations of the aorta. Here reference values in adults for end-diastolic true short axis luminal diameters and areas of the aortic root are presented. Lin et al. have also published reference values for the pulmonary artery using the same MDCT technique (76). Due to the oval shape of the pulmonary artery in true short axis view, averaged pulmonary artery diameters are presented as reference values. Unfortunately, these reference materials could not be used in our study due to the differences in examination techniques.

Although a large majority of the patients with dilated pulmonary artery trunk also had aortic disease (40 out of 47 or 85.1%), a few of these patients (7 out of 47, 14.9%) had no sign of ascending aortic disease, suggesting that pulmonary artery dilatation may be an early marker of vascular disease in MFS patients.

The clinical implications of our findings are important. Pulmonary artery trunk dilatation is common in MFS patients, and does not by itself imply pulmonary hypertension. Dilatation of this vessel in an MFS patient may suggest MFS-related vascular affection even in the absence of visible ascending aortic disease.

9. Conclusions

The general aim of this thesis was to explore the prevalence of different manifestations of Marfan syndrome by using radiological methods, and to evaluate different imaging methods in each organ system examined by radiological methods.

- We found that in spite of a great diversity of combinations in fulfilling the diagnosis according to the Ghent nosology, a combination of the dural major criterion and the presence of genetic major criteria could identify a high percentage (79%) of all affected individuals with MFS in our study population. This indicates an early investigation of dura and genetic major criteria when suspicion of MFS has been raised in adults.
- MR imaging of the lumbosacral spine is encouraged to identify DE and thus strengthen a potential diagnosis of MFS. DE was found in a high percentage of our MFS patients (89% of patients diagnosed as MFS without use of the criterion DE), and has a high specificity for MFS. As much as 16% of the Ghent-positive patients were dependent of DE to fulfill the diagnosis of MFS.
  We suggest that the diagnosis of dural ectasia should be based on the presence of at least one of the following criteria: 1) an anterior meningocele or nerve root sleeve herniation, 2) DSD at level S1 or below larger than DSD at level L4, 3) DSR at level S1 > 0.59.
- CT should be preferred to radiography in the diagnosis of PA. If radiation is a concern, MRI may be used instead of CT. PA was found in more than two thirds of patients with MFS. It has a low sensitivity, but a high specificity for the diagnosis of MFS. Our measurement method CWD for assessment of degree of PA, was found to be robust and highly reproducible, giving a direct measurement of pelvic protrusion irrespective of pelvic shape.
- Pulmonary artery dilatation is a common finding in MFS (54%), and should be assessed using cut-off values based on pulmonary artery diameter measurements in the normal population, and not on nomograms intended for the aorta. MR or CT imaging seems to provide more reliable results for pulmonary artery dimensions than echocardiography. Severe disease of the ascending aorta is a significant predictor of pulmonary artery trunk dilatation in MFS patients, but such dilatation may occur even in the absence of visible aortic disease.

10. Errata

- Paper I, *"Prevalence data on all Ghent features in a cross-sectional study of 87 adults with proven Marfan syndrome",* Discussion, page 1227, second column: It is stated that "Nollen's upper limit of normality for the pulmonary trunk" was 34.8 mm. This is incorrect; it should have been 28.0 mm.

- Paper II, *"Dural Ectasia in Marfan Syndrome: A Case Control Study".* Two errors occur: 1) "Study Population", page 1535, first column: the mean (SD) ages are incorrect, it should have been: mean (SD) age in men 35.1 (11.1) years, and in female 42.1 (13.5) years. 2) "MR Imaging or CT of patients in the Study Population", page 1535, first column: incorrect name of MR unit, it should have been: "Signa LX, GE Healthcare, Milwaukee, Wisconsin".

- Paper III, *"CT of the hips in the investigation of protrusio acetabuli in Marfan syndrome. A case control study".* Discussion, page 1490, first column: It is stated that "Steel et al. studied PA in children and adults with MFS and found different percentages of PA depending on the method of assessment; Steel´s method [12] gave 27% of the patients the diagnosis of PA while the Armbuster method [13] gave 16%". It should have been "Sponseller et al. studied PA in children...."

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12. Papers I - IV

Paper I

Prevalence data on all Ghent features in a cross-sectional study of 87 adults with proven Marfan syndrome

Paper II

Dural Ectasia in Marfan syndrome: A case control study

Paper III

CT of the hips in the investigation of protrusio acetabuli in Marfan syndrome. A case control study

CT of the hips in the investigation of protrusio acetabuli in Marfan syndrome. A case control study

Rigmor Lundby · Eva Kirkhus ·
Svend Rand-Hendriksen · John Hald ·
Are Hugo Pripp · Hans-Jørgen Smith

Abstract
Objectives To establish the prevalence of protrusio acetabuli (PA) in adults fulfilling the Ghent criteria for Marfan syndrome (MFS), and in a normal adult population.
Methods 105 adults with probable MFS and 107 controls were included. CT of the hips was obtained. A qualitative assessment of PA was performed. A new method for estimating the degree of PA was introduced with measurement of the parameter CWD (circle-wall distance). Results were compared to an alternative method based on MRI [1].
Results 87 of the study group fulfilled the Ghent criteria of MFS (Ghent positives), and 18 did not (Ghent negatives). PA was diagnosed qualitatively in 74.7% of Ghent positive persons, in 27.8% of Ghent negative persons, and in 3.7% of the controls. CWD was significantly different between the three groups ($p<0.001$). A slight but significant gender difference was found in Ghent positive persons only. The alternative method did not differentiate between the groups with respect to PA, but showed a significant difference between genders.
Conclusions PA was found significantly more often in MFS persons than in controls. Our method was found to be robust and highly reproducible, giving a direct measurement of pelvic protrusion irrespective of pelvic shape.

Keywords Marfan Syndrome · Computed tomography (CT) · Hip joint · Pelvic bones · Connective tissue diseases

R. Lundby · S. Rand-Hendriksen · H.-J. Smith
Faculty of Medicine, University of Oslo,
Oslo, Norway

R. Lundby (✉) · E. Kirkhus · J. Hald · H.-J. Smith
Department of Radiology and Nuclear Medicine,
Oslo University Hospital, Rikshospitalet,
Sognsvannsvn. 20,
0027 Oslo, Norway
e-mail: rigmor.lundby@medisin.uio.no

S. Rand-Hendriksen
TRS National Resource Centre for Rare Disorders,
Sunnaas Rehabilitation Hospital,
Nesoddtangen, Norway

A. H. Pripp
Biostatistics and Epidemiology Unit, Oslo University Hospital,
Oslo, Norway

Introduction

Protrusio acetabuli (PA) is an inward protrusion of the acetabulum as a rounded mass into the pelvis [2]. Pelvic intrusion and acetabular protrusion seem to be used synonymously. The degree of protrusion varies from a few millimetres to five centimetres [2]. PA is seen in different disorders including primary idiopathic cases and secondary to neoplastic, infectious, metabolic, inflammatory, traumatic, congenital and genetic disorders [3].

PA is one of the eight manifestations that may contribute to the major skeletal criterion for Marfan syndrome (MFS) according to the Ghent nosology [4] (Table 1), and is included as one of the features of the "systemic score" in the newly revised Ghent criteria [5].

A number of radiological features of PA have been suggested, but no gold standard has emerged [6–8]. A newly published study concludes that as pelvic tilt increases, classic radiographic measurements of PA become unreliable, and that computed tomography or magnetic resonance (MR) imaging probably will be more reliable [9].

In this case control study the aims were to establish the prevalence of PA in adult persons fulfilling the Ghent criteria

Table 1 Diagnostic Criteria for Marfan syndrome (MFS) according to the Ghent nosology

System	Major criteria	Criterion for involvement
Skeletal	Requires four of the eight manifestations listed below	Requires two of the eight manifestations in the left column or one manifestation plus two minor criteria
	Manifestations:	Minor criteria
	• Pectus carinatum	• Pectus excavatum of moderate severity
	• Pectus excavatum requiring surgery	• Joint hypermobility (Beighton score≥4)
	• Reduced upper to lower segment ratio<0.85 or Arm span to height ratio greater than 1.05	• Highly arched palate with crowding of teeth
	• Wrist and thumb signs	• Facial appearance (dolicocephaly, malar hypoplasia,
	• Scoliosis of>20° or spondylolisthesis	enopthalmos, retrognathia, down-slanting
	• Reduced extension at the elbows (< 170°)	palpebral fissures)
	• Medial displacement of the medial malleolus causing pes planus	
	• Protrusio acetabuli of any degree	
Ocular	Ectopia lentis	Requires two of the following three minor criteria
		Minor criteria
		• Abnormally flat cornea (< 41,5 dioptres)
		• Increased axial length of the ocular globe (>23,5 mm)
		• Hypoplastic iris or ciliary body
Cardiovascular	• Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva	Requires the presence of at least one major criterion or one minor criterion
	• Dissection of the ascending aorta	Minor criteria
		• Mitral valve prolapse with or without mitral valve regurgitation
		• Dilatation of the main pulmonary artery in the absence of valvular or peripheral pulmonic stenosis or any other obvious cause below the age of 40 years
		• Calcification of the mitral annulus before the age of 40 years
		• Dilatation or dissection of the descending thoracic or abdominal aorta below the age of 50 years
Pulmonary	None	Requires at least one minor criterion
		Minor criteria
		• Spontaneous pneumothorax
		• Apical blebs
Skin and Integument	None	Requires at least one minor criterion
		Minor criteria
		• Striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy or repetitive stress
		• Recurrent or incisional herniae
Dura mater	Major Criterion: • Lumbosacral dural ectasia	None
Genetic	• Having a parent, child or sib who meets these diagnostic criteria independently	None
	• Presence of a mutation in *FBN1* known to cause the Marfan syndrome	
	• Presence of a *FBN1* haplotype around *FBN1,* inherited by descent, known to be associated with unequivocally diagnosed Marfan syndrome in the family	

Confirmation of the diagnosis requires the presence of at least two Major Criteria in two different organ systems and involvement of third organ system. Family history / genetic is counted as an organ system

for MFS, and to find the best criteria for the assessment of PA. CT was chosen due to its direct visualization of the acetabular shape and its superior depiction of cortical bone.

Materials and methods

The study was approved by the Regional Medical Ethics Committee.

For the purpose of informed consent only persons aged above 18 years were included.

Study population

The participants were recruited either by letter sent to the 134 individuals above 18 years of age registered in a National resource centre as having MFS; by advertisement in the journal of the National Association of MFS, or through invitations distributed in the Department of Thoracic and Cardiovascular Surgery at our hospital to patients suspected of having MFS. Age was the only exclusion criterion.

Out of 109 individuals that gave informed consent for participation, one died before the study started; one living abroad was not able to attend, and two withdrew. Consequently, the study population consisted of 105 persons, 67 women aged 20–69 years, mean 41.2 years (SD 13.6), and 38 men aged 19–62 years, mean 35.1 (SD 11.3) years. Before inclusion, 90 had been given a diagnosis of Marfan syndrome; 15 were suspected of having the diagnosis. All participants were Caucasian.

All persons in the study group were assessed for all parts of the Ghent criteria [4] by the same group of physicians. The assessment included sequencing of the entire coding region of the gene *FBN1* and search for large deletions or duplications [10, 11].

Control population

The control cases were chosen from the pool of patients in the radiological archive (PACS) of the Department of Radiology, based on the following criteria: Sex- and age-matched asymptomatic persons with respect to the hips and without any known connective tissue disorder, examined by CT of the abdominal and /or pelvic area due to symptoms from the abdominal area or with suspected vessel disease in the pelvic or abdominal region. Patients with liver or kidney transplants were excluded. The controls included 107 subjects, 68 women aged 19-69 years, mean 40.9 years (SD 13.7), and 39 men aged 19-64 years, mean 35.8 (SD 12.1) years.

CT imaging

Axial CT images with 3 mm slice thickness were obtained in the study population with a GE Prospeed SX CT system (General Electric Medical Systems, Milwaukee, WI, USA) and with different CT systems in the control population.

Image evaluation

The control and study populations were compared in aggregate. Consensus readings of 75 CT examinations of the study group and 77 of the control group were performed by two radiologists (RL and EK). Both were aware of which persons belonged to the study or control group, but had no further clinical information. Thirty CT examinations from each group were interpreted separately by RL and EK for assessment of interobserver agreement. For those without consensus readings, the average of the two radiologists' measurements were used for quantitative data, and for qualitative assessment of whether PA was present, cases with disagreement were resolved by reevaluation in consensus.

Measurements and definitions

PA was diagnosed qualitatively when there was an intrapelvic protrusion of the medial pelvic wall at the level of the acetabulum. The minimum thickness of the acetabular wall was also assessed; and the term "single cortex" was applied when only a single layer of cortical bone could be identified on two or more contiguous 3 mm CT slices (Fig. 1).
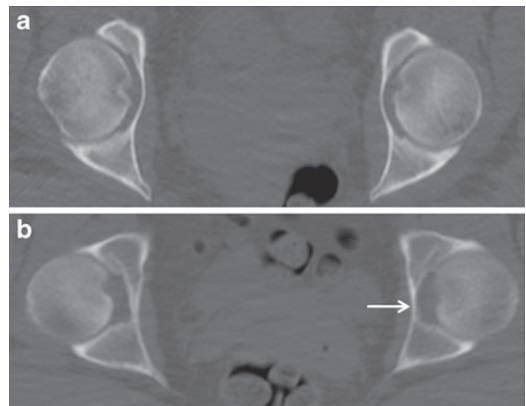

Fig. 1 Axial CT of hips in person with MFS (**a**) and normal control (**b**). **a** Bilateral protrusio acetabuli and only one cortical bone layer, "single cortex". **b** Normal hips. Single cortex in left hip (*arrow*)

For quantification of PA we introduced a circle with 10 cm radius. The circle was fitted to the inner pelvic wall at the level of the acetabulum where the cranial border of the superior pubic ramus fuses with the anterior column of the acetabulum (Fig. 2). This level usually also includes the fovea of the femoral head. The circle was adjusted to a best fit with the concavities of the inner walls of the anterior and posterior column of the acetabulum. The distance between the line of the circle and the medial most point of the inner pelvic wall of the acetabular fossa (circle-wall distance, CWD) was measured (Fig. 2). A positive distance indicates that this medial most point is medial to the circle, and a negative distance that the inner acetabular wall extends lateral to the circle. Increasing degrees of PA have increasing positive values of CWD.

Quantification of PA was also done according to the method described by Chen et al. [1]. In compliance with this method, the "distance between the medial most point of the acetabular fossa and a line perpendicular to the horizontal axis that passes through the lateral most point of the posterior inner pelvic wall" was measured at the level of the ischial spine. We named this distance the "fossa-line distance" (FLD). For easier comparison of the two methods, we decided to let positive values indicate PA, in contrast to Chen et al. who used negative values to indicate protrusion.

Statistics

Continuous data were described as mean and standard deviation or median, interquartile range and range for
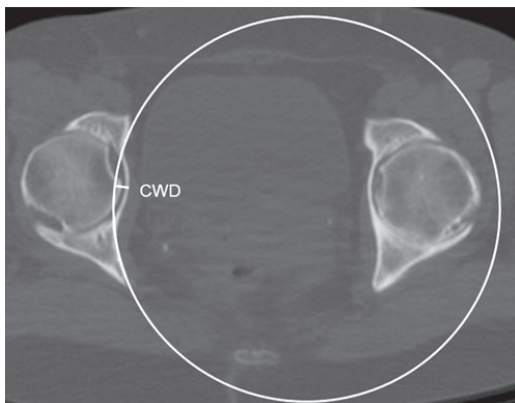

Fig. 2 Axial CT of hips in a case of MFS with bilateral PA. A 10 cm radius circle is adapted to the inner acetabular wall of the right hip, and measurement of CWD is indicated. Osteoarthritis in left hip

normally distributed or skewed data, respectively. Categorical data were described as frequency and percentage. Differences between the study groups were analyzed with one-way ANOVA with post hoc multiple comparison using Bonferroni correction or Pearson chi-square tests as appropriate. Skewed data were analyzed with a nonparametric Kruskal-Wallis test. Interobserver agreement was evaluated with intraclass correlation coefficient for continuous data and kappa statistics for categorical data. Receiver operating characteristic (ROC) curves were constructed to assess the ability of CWD to differentiate MFS from controls and PA from normal hips. Significance level was set to 5%. All statistical analyses were performed by SPSS version 16.0 (SPSS, Chicago, Il).

Results

The study population was divided into two groups through the clinical assessment for MFS: 1) persons fulfilling the Ghent criteria (Ghent positive, $n=87$), and 2) persons suspected of having MFS, but not fulfilling the Ghent criteria (Ghent negative, $n=18$). The control population constituted the third group ($n=107$).

PA was diagnosed qualitatively on one or both sides in 74.7% of Ghent positive persons, in 27.8% of Ghent negative persons, and in 3.7% of the controls (Table 2). None of the participants were dependent on a diagnosis of PA to become Ghent positive. PA, when present, was bilateral in 81.5% of Ghent positive persons, in 100% of Ghent negative persons, and in 50% of controls.

Quantitative assessment of acetabular protrusion using the 10 cm circle was possible in all study persons and controls. Measurement of CWD showed statistically significant differences between the three groups (Table 2). The median CWD was 3 mm (range 0.0–9.0 mm) in Ghent positive persons, 0 mm (range -0.5–5.0 mm) in Ghent negative persons, and 0 mm (range -3.0–2.0 mm) in controls. ROC analysis of CWD vs. qualitative diagnosis of PA showed an area under the curve of 0.99 (95% CI 0.98–1.0); a CWD cut-off value of 1.25 mm resulted in a sensitivity and specificity for PA of 95.5% and 97.6%, respectively. ROC analysis of CWD in differentiating MFS from controls showed a sensitivity and specificity in diagnosing MFS of 68.8% and 97.2%, respectively, when using a CWD cut-off value of 1.25 mm (Fig. 3).

Measurement of acetabular protrusion according to Chen et al. [1] was possible in 146 (68.9%) of all study persons and controls. No statistically significant differences between the three groups were found. The median FLD was 0.0 mm (range -7.0–8.0 mm) in Ghent positive persons, 0.25 mm (range -3.0–3.0 mm) in Ghent negative persons, and 0.0 mm (-7.0–6.0 mm) in controls.

Table 2 Characteristics of the Ghent positive persons, Ghent negative persons, and controls, in total 212 persons and 420 assessable hips (4 total hip prostheses)

Characteristics	Ghent positives	Ghent negatives	Controls	P value
No. of hips (persons)	170 (87)	36 (18)	214 (107)	
Age [mean (SD)]	39.6 (13.0)	36.1 (13.4)	39.0 (13.3)	0.592
Females [n (%)]	56 (64.4%)	11 (61.1%)	68 (63.6%)	0.966
PA qualitative method, number (percent) of group	65 (74.7%)	5 (27.8%)	4 (3.7%)	< 0.001
PA qualitative method, number (percent) of hips	116 (68.2%)	10 (27.8%)	6 (2.8%)	< 0.001
Single cortex, number (percent) of hips	159 (93.5%)	25 (69.4%)	109 (50.9%)	< 0.001
CWD, Circle method on hips, mm [median (min, max)]	3.0 (0.0, 9.0)	0.0 (−0.5, 5.0)	0.0 (−3,0 2.0)	< 0.001
FLD, Chen method on hips, mm [median (min, max)]	0.0 (−7.0, 8.0) $n=116$	0.25 (−3.0, 3.0) $n=20$	0.0 (−7.0, 6.0) $n=144$	0.322

If n is specified in a cell, the number of hips included in that measurement is different from the number included in the study. *PA* protrusio acetabuli, *CWD* circle-wall distance, *FLD* fossa-line distance

Statistically significant differences between women and men were found in all three groups when using the Chen method (Fig. 4). Median FLDs in women and men, respectively, were 1.0 and 0.0 mm in Ghent positive persons; 1.0 and −2.0 mm in controls. Relatively large positive values of FLD could be found in women also in the absence of PA (Fig. 5).

With our circle method, significant gender differences were not found, except for the Ghent positive persons where women had slightly larger median CWDs than men (3.0 vs. 2.0 mm).

"Single cortex" was found on at least one side in 94.3% of Ghent positive persons, in 83.3% of Ghent negative persons, and in 57% of the controls. When presence of "single cortex" was calculated as percentage of number of hips, the figures for these three groups were 93.5%, 69.4%,

and 50.9%, respectively. These differences between the groups were statistically significant (Table 2).

Interobserver study

The interobserver agreement for assessing PA qualitatively was high with a kappa value (κ) of 0.88 (95% CI 0.81–0.95) for the right hip and 0.92 (CI 0.81–1.0) for the left hip. The circle method had an interclass correlation coefficient (ICC) of 0.91 (95% CI 0.89–0.95) and 0.89 (95% CI 0.81–0.93) on the right and left side, respectively. For the Chen method, ICC was 0.95 (95% CI 0.91–0.97) and 0.94 (95% CI 0.90–0.97) on the right and left side, respectively. The kappa value (κ) for assessment of single cortex was 0.84 (CI 0.69–0.99) for the right hip and 0.83 (CI 0.67–0.99) for the left hip.
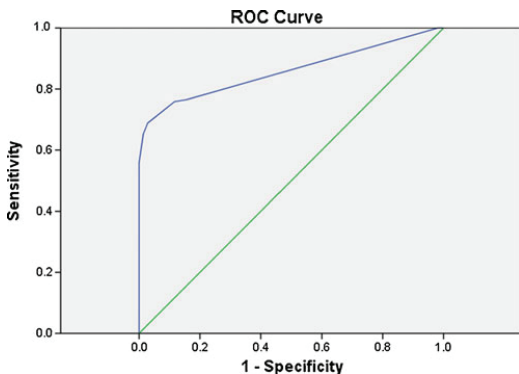

Fig. 3 ROC curve of CWD as a marker of MFS when comparing Ghent positive patients and controls
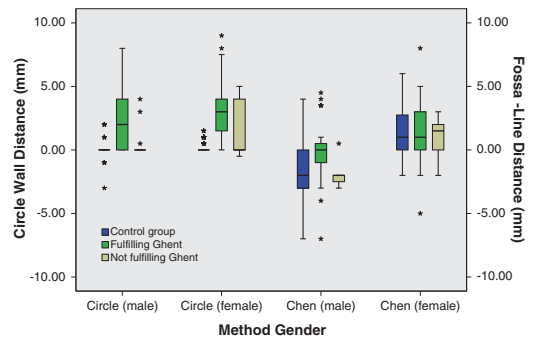

Fig. 4 Boxplots showing median, interquartile distance and range of circle-wall distance (CWD) measured with Circle method and fossa-line distance (FLD) measured with Chen's method [1], for males and females, respectively
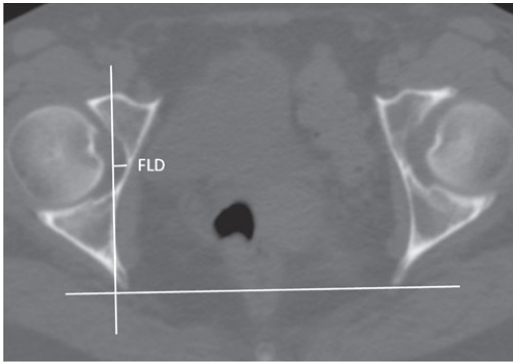
Fig. 5 Axial CT of the hips in female control. Relatively large FLD (5.5 mm), but no protrusio acetabuli. Lines drawn according to method by Chen et al [1]

Discussion

PA is one of the manifestations that may contribute to the diagnosis of MFS [4], however, diagnosing PA has been a point of discussion since the accuracy of measurements on plain pelvic radiographs is uncertain and may vary with pelvic tilt [9]. Few authors have assessed the different radiological methods in a validated way [9], and the definition of PA has varied depending on the radiological method used [8].

The reported prevalence of PA in MFS has varied in different studies [7]. Steel et al. studied PA in children and adults with MFS and found different percentages of PA depending on the method of assessment; Steel´s method [12] gave 27% of the patients the diagnosis of PA while the Armbuster method [13] gave 16%. Yule et al. [6] found that 60% of their MFS patients had PA using the relationship of the acetabular line to the ilioischial line as the sole criterion of PA. In their study, 7% of the controls had PA based on this method.

Qualitative assessment of PA in our study was defined as any degree of intrapelvic protrusion of the medial pelvic wall at the level of the acetabulum. Using this criterion, we found a very high percentage of PA in our MFS persons (74.7%) as compared to the controls (3.7%). The finding of PA in 27.8% of the persons suspected of having MFS but not fulfilling the Ghent criteria, probably reflects that several of these persons had other connective tissue diseases that might predispose for PA. Of the 18 persons, five had Loeys-Dietz syndrome; one vascular Ehlers-Danlos syndrome, and one homocystinuria [11].

For quantitative assessment of differences in medial protrusion of the acetabulum we developed the "circle method" with a standard radius. The method was quick and easy to apply, with a high interobserver reproducibility. We found a 10 cm radius circle to have an arc similar to the concavity of the inner pelvic wall at the acetabulum in most normal adults. The vast majority of the controls therefore had no distance between the circle and the medial pelvic wall at this level, i.e. a CWD of 0 mm. A threshold value for CWD with respect to PA occurs when the inner pelvic acetabular wall is flat. The actual CWD in these cases will vary slightly with the anteroposterior size of the acetabulum, i.e. with the distance between the two points where the circle crosses the acetabular wall anteriorly and posteriorly. We found this distance to be in the order of 3–3.5 cm, corresponding to a CWD of 1.1–1.5 mm. Our ROC analysis suggested a cut-off value of 1.25 mm.

Measurement of CWD with our circle method confirmed a statistically significant difference between the three groups, PA being both more frequent and more severe in Ghent positive persons, with a maximum CWD of 9.0 mm as compared to 5.0 mm and 2.0 mm in Ghent negative persons and controls, respectively. Due to the fact that approximately 25% of the Ghent positive persons did not have PA, CWD was not a very sensitive marker of MFS (Fig. 3). The less than 100% specificity with the optimum cut-off value of CWD reflects the finding that even presumed normals may have a slight degree of PA.

The quantitative method for assessment of PA as described by Chen et al. [1] could be applied in approximately two thirds of the cases, the main reason for failure being considerable asymmetry and pelvic tilt. Chen's method requires that the ischial spine is depicted in the same axial image as the medial most point of the acetabular fossa, and this was often not the case. When the method could be used, it had a high interobserver reproducibility, but a low accuracy in detecting PA. Somewhat unexpectedly, Chen's method showed significant gender differences not shown by our circle method (except in the Ghent positive persons). This may be explained by a difference in pelvic shape between genders. The pelvic outlet in women tends to be wider than in men, resulting in a higher degree of convergence of the anterior pelvic walls. In addition, women have increased backward sacral tilt compared to men [14], which will enhance anterior convergence. A high anterior convergence can make the acetabulum project medial to the inner pelvic wall of the posterior column (Fig. 5), giving a false impression of PA.

Our circle method is not influenced by anterior convergence of the pelvic walls, and the slight gender difference in CWD found with this method in Ghent positive persons, may therefore reflect a real difference between the sexes with respect to development of PA in MFS.

We found bilateral PA more often in Ghent positive persons than in the controls, probably reflecting that MFS is a systemic disorder which is likely to affect both hips with the same frequency.

The finding of "single cortex" for the acetabulum was always present in cases of PA. It seems likely that the same

mechanism that leads to inward protrusion of the acetabular wall also will result in thinning of the wall. "Single cortex" was however observed also in hips without PA as more than half of our normal controls (57%) had "single cortex" of the acetabulum, but in a smaller part of the acetabular wall compared to hips with PA (Fig. 1).

Our study has several limitations. The choice of a 10 cm radius circle for measuring the degree of protrusion was somewhat arbitrary, adjusted to the concavity of the inner acetabular wall of most adult hips. This inner concavity is not always uniform; the curvature of the arc may change from anterior to posterior. In cases of PA, when the circle crosses the inner pelvic acetabular wall at two points, the value of CWD is not only dependent on the degree of PA, but also on the distance between the crossing points, which again is determined by the placement of the circle. Our interobserver study indicates, however, that placement of the circle and measurement of CWD could be done with high reproducibility. Using a somewhat larger circle in adults would have had minor influence on the results. Replacing the 10 cm circle with e.g. a 12 cm circle would have changed the threshold values of CWD (a flat inner pelvic acetabular wall) from 1.1–1.5 mm (see above) to 1.0–1.3 mm. A smaller circle would have to be used for similar measurements in children. When testing a new method for accuracy, it should ideally be compared to an independent and established gold standard. In this case, there was no such gold standard, and the sensitivity and specificity of the circle method in diagnosing PA, was therefore calculated using qualitative assessment of PA with CT as gold standard.

CT of the hips can be performed with low radiation dosage, but persons with hereditary connective tissue diseases are often subject to diagnostic procedures, and methods using ionizing radiation should be kept to a minimum. MR imaging would probably have given similar results with respect to assessment of PA.

Conclusions

PA was found significantly more often in MFS persons than in controls. Our circle method was found to be robust and highly reproducible, giving a direct measurement of the degree of pelvic protrusion irrespective of pelvic shape. CT gives an excellent view of the hips, and should be preferred to radiography in the diagnosis of PA.

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Paper IV

The pulmonary artery in Marfan syndrome patients.
A cross-sectional study

The pulmonary artery in Marfan syndrome patients. A cross-sectional study

Rigmor Lundby[1,2], Svend Rand-Hendriksen[1,3], John K. Hald[2], Are Hugo Pripp[4], Hans-Jørgen Smith[1,2]

[1]Faculty of Medicine, University of Oslo, Oslo, Norway

[2]Department of radiology and nuclear medicine, Oslo University Hospital, Oslo, Norway

[3]TRS National Resource Centre for Rare Disorders, Sunnaas Rehabilitation Hospital, Nesoddtangen, Norway

[4]Biostatistics and Epidemiology Unit, Oslo University Hospital, Oslo, Norway

Corresponding author:

Rigmor Lundby

Address: Department of radiology and nuclear medicine, Oslo University Hospital, Rikshospitalet, Sognsvannsveien 20, N-0027 Oslo, Norway

e-mail: rigmor.lundby@medisin.uio.no

Abstract

Objectives To establish the prevalence of pulmonary artery dilatation in Marfan syndrome (MFS) by modern radiological methods, to correlate diameter of the vessel with aortic disease, and explore predictors of pulmonary artery dilatation in MFS.

Methods MR or CT imaging of the pulmonary artery and aorta was performed in 87 patients with proven MFS. Diameters of the pulmonary artery root and trunk, and of the aortic root were measured perpendicular to the long axis of the vessels; pulmonary artery diameters on axial images, and aortic diameters on oblique sagittal images.

Results Compared to normal values in the literature, 47 of the 87 patients (54%) had widened pulmonary artery trunk (≥ 30 mm). Of these 47, 15% had no sign of ascending aortic disease. The mean (SD) ratio between pulmonary artery root and trunk diameters was 1.18 (0.155). Multivariate analysis showed that ascending aortic surgery and high BSA were associated with dilatation of the pulmonary artery trunk.

Conclusions Pulmonary artery dilatation is found in a high proportion of MFS patients, and should be assessed using cut-off values based on pulmonary artery diameter measurements in the normal population. Severe disease of the ascending aorta is a significant predictor of pulmonary artery trunk dilatation in MFS patients.

Keywords

Introduction

Marfan syndrome (MFS) is an autosomal dominant genetic connective tissue disorder characterized by manifestations in many organ systems, stated in the Ghent criteria from 1996 ("Ghent 1 criteria") [1]. The diagnosis is based on findings in skeleton, eyes, the cardiovascular and pulmonary systems, the skin and integument, dura, a family history, and mutations in the gene encoding for fibrillin one (*FBN1*) [1, 2]. A major and frequent cardiovascular criterion of MFS is dilatation of the ascending aorta and aortic root. To fulfil the major cardiovascular criterion in the Ghent nosology, the aortic root and/or ascending aorta must be affected.

According to the Ghent nosology from 1996 "dilatation of the main pulmonary artery, in the absence of valvular or peripheral pulmonary stenosis or any other obvious cause, below the age of 40 years" is considered a minor cardiovascular criterion of MFS [1]. Although dilatation of the aortic root and pulmonary artery often are coexistent [3], it has been suggested that pulmonary artery dilatation may be a sign of cardiovascular involvement in MFS patients even in the absence of aortic disease [3].

Dilatation of the pulmonary artery is described as a sign of MFS in many articles [1, 3-7], but documentation of the proportion of patients with dilated pulmonary artery in the MFS population with modern radiological methods, is sparse. Revised Ghent criteria were published in 2010 ("Ghent 2 criteria") [8], and here dilatation of the pulmonary artery is not included. Lack of specificity and incomplete knowledge of threshold values for dilatation of the pulmonary artery are among the reasons for excluding dilatation of this structure from the Ghent criteria. Further research was recommended.

In the present study, the axial diameters of the pulmonary artery root and trunk and the oblique sagittal diameter of the aortic root were measured with MR imaging or CT in a cohort of 87 patients with proven MFS without other known causes of pulmonary artery dilatation. Measurements were compared to normal values based on MR and CT in the literature. The aims were to find the prevalence of dilated pulmonary artery in MFS, to correlate diameters of the vessel with aortic disease, and to explore predictors of pulmonary artery dilatation in MFS.

Materials & Methods

The study was approved by the regional medical ethics committee; and for the purpose of informed consent, only patients older than 18 years of age were included.

None of the patients were suspected of having pulmonary hypertension.

Study population

The participants were recruited either by letter sent to the 134 individuals above 18 years of age registered in a National resource centre as having MFS; by advertisement in the journal of the National Association of MFS, or through invitations distributed in the Department of Thoracic and Cardiovascular Surgery at our hospital to patients suspected of having MFS. Age was the only exclusion criterion before the examinations. Out of 109 individuals that gave informed consent for participation, one died before the study started; one living abroad was not able to attend, and two withdrew. All 105 participants were Caucasian. All patients were assessed for all parts of the Ghent criteria (Ghent 1) [1] by the same group of physicians. For assessment of fulfilment of the major cardiovascular criterion in the Ghent nosology, information about previous surgery due to dilatation or dissection of the ascending aorta, and dilatation of the ascending aorta measured with echocardiography was used [1, 9].The assessment of Ghent criteria included sequencing of the entire coding region of the gene *FBN1* and search for large deletions or duplications [9].

MR or CT of the aorta and pulmonary artery

This study was a substudy of the "Norwegian Marfan Study". In this part of the study MR imaging of the aorta and the pulmonary artery was performed unless contraindicated when CT examinations were obtained instead.

MR imaging at 1.5 T (Signa LX, GE Healthcare, Milwaukee, Wisconsin) of the aorta and pulmonary artery in axial and oblique sagittal planes was performed using a standard ECG-gated T1-weighted SE sequence. Repetition time equalled the R–R interval, echo time was minimum 9.32 ms to maximum 39.976 ms, slice thickness was 7 mm in the axial plane, and 4 mm in the oblique sagittal plane.

Non-enhanced axial CT images with 5 mm slice thickness were obtained on a ProSpeed SX scanner (GE Healthcare, Milwaukee, Wisconsin) in patients in whom MRI was contraindicated. As part of assessment of all Ghent criteria, HRCT of the lungs was performed as well.

Measurements and estimations

Consensus readings were performed by two radiologists (HJS and RL) of all MR and CT examinations. Aortic dimensions were assessed perpendicular to the long axis of the vessel on oblique sagittal images at the level of the sinuses of Valsalva (aortic root). Main pulmonary

artery dimensions were assessed perpendicular to the long axis of the artery on axial images at two levels: the pulmonary artery root, and the pulmonary artery trunk at the pulmonary artery bifurcation (Fig. 1).
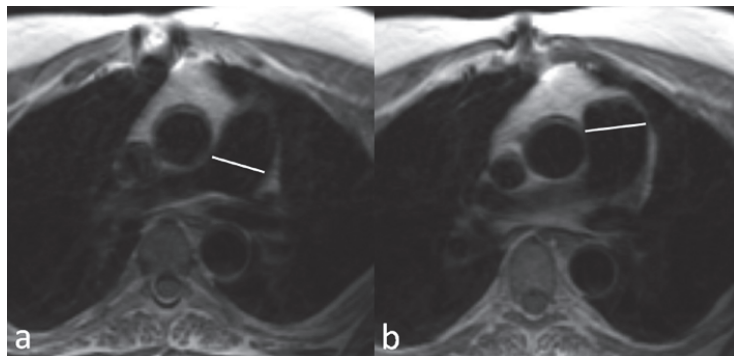

Figure 1. Axial MR images of 63-year-old male MFS patient. Diameter measurement of the pulmonary artery trunk (a) and pulmonary artery root (b) is indicated. The ascending aorta is replaced by a graft.

In the present substudy, fulfilment of the major cardiovascular criterion for MFS was reassessed using MR or CT measurements of all native ascending aortas. The aortic root diameter and body surface area (BSA) for each participant were plotted in Roman et al.´s nomogram [1, 10].

This major criterion was also considered fulfilled in participants having previous surgery on the ascending aorta due to dilatation or dissection.

Assessment of pulmonary artery dilatation (root and trunk) according to Ghent 1 criteria was performed using nomograms for the aortic root [1]. Pulmonary artery trunk dilatation was reassessed by comparison with recently published data on normal values based on 5 mm axial CT imaging, suggesting a mean diameter of 24.0 mm and an upper limit of 29.6 mm (24.0 mm + 2 SD) for the normal pulmonary artery trunk in adults [11]. Using an electronic calliper with 1 mm increments, we defined pulmonary trunk dilatation as diameters $\geq$ 30 mm in our reassessment.

Statistics

Data were described as mean (standard deviation) or frequency (percentage) for continuous or categorical variables, respectively. Univariate statistical analysis on differences between groups were analysed with independent sample t-test or chi-square, as appropriate, and correlation assessed with Pearson correlation coefficient. Multivariate analysis on factors influencing pulmonary artery diameter was done with a multiple linear model. The statistical

level of significance was 5%. All analyses were conducted with SPSS version 18 (SPSS Inc, Chicago, IL).

Results

Eighty-seven out of 105 persons (56 female) fulfilled the Ghent 1 criteria for MFS, and in the present substudy of a national Marfan Study, these 87 persons constituted the study group. The mean (SD) age in men were 35.1 (11.1) years, and in female 42.1 (13.5) years. Characteristics of the study population are given in Table 1.

Table 1. Characteristics of study population given as mean (SD) or number of patients (percentage). Diameters measured by MR or CT.

Patient characteristics	
Number of patients	87
Female	56 (64.4%)
Age (years)	39.6 (13.0)
Weight (kg)	82.7 (17.3)
Height (cm)	184.2 (10.6)
BSA (m^2)	2.07 (0.24)
BMI (kg/cm^2)	24.7(4.38)
Diameter of aortic roots (mm) without previous aortic surgery, n=56	36.6 (6.9)
Patients with previous surgery on ascending aorta	30 (34.5%)
Pulmonary artery root diameter (mm), n=86	35.0 (4.6)
Pulmonary artery trunk diameter (mm)	29.8 (3.8)
Pulmonary artery trunks widened according to Ghent 1 criteria (1996)	0
Pulmonary artery roots widened according to Ghent 1 criteria (1996)	7
Pulmonary artery trunks widened according to cut-off 30 mm	47 (54%)
Pulmonary artery roots widened according to cut-off 34.8 mm, n=86	43 (50%)

MR imaging was contraindicated in six persons, and CT was therefore performed instead. In five of the 81 thoracic MR examinations of the study group, image quality was inadequate for measurement of pulmonary artery dimensions; in these five cases HRCT was available for diameter measurements. In one of the 87 patients neither MR nor CT had adequate depiction of the pulmonary artery root, and the diameter could therefore not be measured.

MR and CT measurements of the pulmonary artery showed mean (SD) diameters of the pulmonary artery root and trunk of 35.0 (4.6) mm and 29.8 (3.8) mm, respectively. The pulmonary artery root was found to have larger diameter than the trunk in most cases, and the mean (SD, range) ratio between the pulmonary artery root and trunk was 1.18 (0.155, 0.78-1.58).

According to Ghent 1 criteria for pulmonary artery dilatation [1], which are based on nomograms of the aortic root, 7 out of 39 patients (17.9%) under 40 years of age had dilated pulmonary artery root, while none had dilatation of the pulmonary artery trunk. Compared to published normal values for adult pulmonary artery trunk diameters [11], 47 (54%) of the 87 patients had dilated pulmonary artery trunk with a diameter $\geq$ 30 mm.

Thirty (34.5 %) of the 87 persons had previous surgery on the ascending aorta. Echocardiographic measurements in the remaining 57 patients showed that 16 of these patients had dilated aortic root according to the Ghent 1 criteria (nomograms by Roman et al.) [9], however, when the aortic root diameters were reassessed with MR or CT, 40 of the 57 aortic roots were found to be dilated. Based on MR or CT a total of 70 (80.5%) patients thus fulfilled the major cardiovascular criterion for MFS. The MR or CT measured mean (SD) aortic root diameter in the 57 patients with native ascending aorta was 41.3 (6.1) mm. Seven (14.9%) of the 47 patients with pulmonary artery trunk diameter $\geq$ 30 mm had normal diameter of the aortic root, 20 (42.6%) had a dilated native aortic root, and 20 (42.6%) had previous surgery on the ascending aorta.

Table 2. Pulmonary artery diameters in relation to patient characteristics.

	Diameter of pulmonary artery root, n = 86	p-value pulmonary artery root	Diameter of pulmonary artery trunk, n = 87	p-value pulmonary artery trunk
Gender, mean (SD) mm				
Male	36.2 (4.2)	0.063	29.9 (3.1)	0.932
Female	34.4 (4.7)		29.8 (4.2)	
Age, correlation	0.300	0.005	0.182	0.091
Height, correlation	0.261	0.015	0.147	0.173
Weight, correlation	0.425	< 0.001	0.353	0.001
BMI, correlation	0.265	0.014	0.185	0.086
BSA, correlation	0.385	< 0.001	0.285	0.007
Previous surgery ascending aorta, mean (SD) mm				
Yes	36.5 (5.1)	0.035	31.32 (4.7)	0.017
No	34.2 (4.1)		29.0 (3.0)	

There were no significant differences between genders with respect to pulmonary artery diameters, but a tendency towards larger pulmonary artery root diameters in men (p=0.063) (Table 2). The pulmonary artery root diameters correlated significantly with age, height, weight, BMI and BSA, while the pulmonary artery trunk diameters had significant positive

correlation with weight and BSA only (Table 2). Pulmonary artery root and trunk diameters were significantly larger in patients with previous surgery on the ascending aorta compared to those without such surgery (p=0.041 and p=0.027, respectively) (Table 2). Pulmonary artery trunk diameters were significantly larger in patients with ascending aortic disease (dilatation or previous surgery) than in those without (p=0.018), but the pulmonary artery root diameters were not significantly larger in this patient group (p=0.104).

A multivariate analysis of variables that potentially may have influenced the pulmonary artery root and trunk diameters is shown in Table 3. For the pulmonary artery root, age (p=0.009) and BSA (p=0.028) were the only parameters which correlated significantly with the vessel diameter. Previous surgery on the ascending aorta (p=0.005) and BSA (p=0.004) correlated significantly with the pulmonary artery trunk diameter.

Table 3. Multivariate analysis of variables that might affect pulmonary artery diameters.

A. Dependent variable: diameter of pulmonary artery root

Parameter	Coeffient (95% CI)	p-value
Ascending aorta		
Dilated	0.73 (-1.68; 3.15)	0.55
Previous surgery	2.00 (-0.54; 4.54)	0.12
Male gender	0.77 (-1.67; 3.22)	0.53
Age	0.098 (0.025; 0.17)	0.009
BSA	5.38 (0.60; 10.16)	0.028
BMI	0.13 (-0.098; 0.35)	0.27

B. Dependent variable: diameter of the pulmonary artery trunk.

Parameter	Coeffient (95% CI)	p-value
Ascending aorta		
Dilated	1.68 (-0.42; 3.77)	0.12
Previous surgery	3.18 (-0.97; 5.39)	0.005
Male gender	-1.96 (-4.08; 0.16)	0.07
Age	0.02 (-0.04; 0.09)	0.48
BSA	6.2 (2.03; 10.36)	0.004
BMI	0.017 (-0.18; 0.21)	0.86

Discussion

Our study showed that when compared to normal values in healthy adult persons [11], more than half (54%) of our adult patients with proven MFS had dilatation of the pulmonary artery trunk, some (approx. 15%) even in the absence of dilatation of the aortic root or ascending aorta.

The Ghent 1 criteria of 1996 [1] included dilatation of the pulmonary artery as a sign (minor vascular criterion) of MFS, but in the revised criteria (Ghent 2) published in 2010 [8], this criterion was omitted. Reasons given were that pulmonary artery dilatation is not specific to the diagnosis of MFS, that complications of pulmonary artery disease are rarely seen, and that further research is needed regarding thresholds and the diagnostic utility of this finding [8] . The uncertainty regarding threshold values for pulmonary artery dilatation is partly caused by the vagueness of the Ghent 1 criteria with respect to the pulmonary artery. The authors state that "until normal values for pulmonary artery diameter are available, dilatation can be detected provisionally by echocardiography, CT or MRI using nomograms for the aorta" [1]. Furthermore, the Ghent 1 criteria do not specify which part of the pulmonary artery should be measured, the root or the trunk.

In our study of 87 MFS patients, we measured the pulmonary artery root and trunk diameters on axial 7 mm or 5 mm slices based on MR (7 mm) or CT (5 mm). In the literature, most papers addressing upper normal values for the pulmonary artery have considered the pulmonary artery trunk only, and among those performed with axial imaging [4, 11-14], only three have included an adequate number of subjects (Table 4). The upper normal limit for the pulmonary artery trunk diameter, defined as mean diameter + 2 SD, was quite similar in two of the studies [12, 13], 32.4 and 33.2 mm, respectively, and clearly larger than in the third study [11], 29.6 mm. This may be explained by the difference in slice thickness, 10 mm vs. 5 mm. axial slices will cut the main pulmonary artery obliquely, and thicker slices are apt to overestimate the diameter due to partial volume effects. The 126 subjects studied by Bozlar et al. [11] were imaged with nearly the same slice thickness as our MFS patients, and the age distribution was furthermore similar, 30.6 ± 7.9 years and 35.1 ± 11 years, respectively. Pulmonary hypertension and thoracic pathology had been excluded. We therefore consider this group of healthy adults as an adequate control group for our study.

Table 4. Literature review of normal pulmonary artery (PA) trunk diameters based on axial CT or MR imaging.

Reference	Subjects (n)	Age, mean (SD) years	Modality / slice thickness	PA trunk diam. mean ± SD mm	PA trunk upper limit, mean + 2SD
Karazincir et al. 2008 (13)	112	46.3 ± 13.6	CT / 10 mm	26.6 ± 2.9	32.4
Bozlar et al. 2007 (11)	126	30.6 ± 7.9	CT / 5 mm	24.0 ± 2.8	29.6
Nollen et al. 2002 (4)	15	28.0 ± 4.0	MR / unknown	24.0 ± 2.0	28.0
Choe at al. 2000 (14)	10	Unknown, range 25-72	CT / 10 mm	25.6 ± 2.2	30.0
Edwards et al. 1998 (12)	100	Unknown, range 11-90	CT / 10 mm	27.2 ± 3.0	33.2

Normal values for the pulmonary artery root diameter are nearly non-existing in the literature. Nollen et al. measured diameters of the pulmonary artery root and trunk in 50 MFS patients and 15 controls using MR imaging. Their pulmonary artery root diameters were not perpendicular to the long axis of the vessel, however, instead three separate oblique diameters in the axial plane were measured, and the anterior right diameter was used for analysis [4]. They suggested an upper normal value for the pulmonary artery root of 34.8 mm based on this diameter. Using this cut-off value, 50% (43 of 86) of our MFS patients had dilated pulmonary artery root (Table 1). The pulmonary artery root diameter in MFS patients and controls has also been assessed with echocardiography, and based on ROC analysis, a cut-off value for discriminating between normals and MFS of 23 mm was suggested for subjects older than 14 years [3]. This is clearly a much smaller value than the upper limit suggested by Nollen et al. [4] (34.8 mm) and the mean value in our MFS patients (35.0 mm), probably reflecting the inherent differences between the modalities used. Measurements comparable to those obtained with axial CT or MR imaging may be difficult to obtain with echocardiography where the imaging plane is dependent on the acoustic window. This difficulty is underscored by our own study. Our preliminary measurements of aortic root diameters were performed with echocardiography and resulted in 16 out of 57 MFS patients having dilated aortic root. When remeasured with MR or CT, the number increased to 40 of 57.

The large discrepancy between the findings of pulmonary artery dilatation using nomograms for the aorta as recommended by Ghent 1 [1] and when using cut-off values based on 2 SD above the mean value in healthy volunteers, suggests that nomograms for the aorta are not suited for assessment of pulmonary artery dilatation. In the normal population, the pulmonary

artery trunk is on average smaller than the ascending aorta, but the variation is large. In a recent multidetector CT study of 103 normal, healthy adults, the ratio of short axis pulmonary trunk diameter to short axis ascending aorta was mean (SD) 0.89 (0.24) [15].

The aortic and pulmonary artery roots have a common embryologic origin [16], and since aortic root dilatation is typical of MFS, it has been speculated that the pulmonary artery root is the most likely part of the vessel to dilate [3, 4]. There is sparse evidence only of this in the literature. In an MR study of 50 adult MFS patients and 15 adult controls [4], the pulmonary artery root was found to be wider than the pulmonary artery trunk in both patients and controls; the difference between root and trunk was, however, larger in MFS patients than in controls [4]. The pulmonary artery root being wider than the trunk is confirmed by our own study, mean (SD) diameters being 35.0 (4.6) and 29.8 (3.8), respectively.

The above findings and speculations could indicate that pulmonary artery root dilatation is more strongly correlated to disease of the ascending aorta in MFS patients than is pulmonary artery trunk dilatation. This was not confirmed by our study. Both the pulmonary artery root and trunk were significantly larger in the patients with previous surgery on the ascending aorta than in those without previous surgery, probably reflecting a correlation between pulmonary artery dilatation and the most severe cases of aortic disease in MFS. However, when comparing pulmonary artery diameters in patients fulfilling the major cardiovascular criterion (surgery or dilatation of the aortic root or ascending aorta) and those not fulfilling the criterion, only the pulmonary artery trunk was significantly larger in patients fulfilling the criterion. A correlation between aortic disease and pulmonary artery trunk diameter was also suggested by our multivariate analysis showing that previous surgery on the ascending aorta was a significant predictor of pulmonary artery trunk dilatation, but not of pulmonary artery root dilatation.

Although a large majority of the patients with dilated pulmonary artery trunk also had aortic disease (40 out of 47 or 85.1%), a few of these patients (7 out of 47, 14.9%) had no sign of ascending aortic disease, suggesting that pulmonary artery dilatation may be an early marker of vascular disease in MFS patients.

The clinical implications of our findings are few, but important. Pulmonary artery trunk dilatation is common in MFS patients, and does not by itself imply pulmonary hypertension. Dilatation of this vessel in a MFS patient may suggest MFS-related vascular affection even in the absence of visible ascending aortic disease.

Limitations

A major limitation of our study is lack of controls using the exact same imaging technique as for our patients. Some relevant and high quality studies of healthy adults using similar technique as ours have been published, however, and we believe that normal values for pulmonary artery trunk diameter using axial imaging are now well documented [11]. Reliable normal values for pulmonary artery root diameter are still missing, however, and may be difficult to obtain given the asymmetry of this part of the vessel.

Our study was performed in the period 2002 – 2004, and MR techniques for non-enhanced imaging of thoracic vessels have improved since then. Multi-slice ECG-triggered MR imaging also introduces a small variation in vessel diameter due to imaging of the vessel at different time points during the cardiac cycle.

Conclusions

Pulmonary artery dilatation is a common finding in MFS (54%), and should be assessed using cut-off values based on pulmonary artery diameter measurements in the normal population, not on nomograms intended for the aorta. MR or CT imaging seems to provide more reliable results for pulmonary artery dimensions than echocardiography. Severe disease of the ascending aorta is a significant predictor of pulmonary artery trunk dilatation in MFS patients, but such dilatation may occur even in the absence of visible aortic disease.

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