

# Marfan Syndrome

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[Abstract](#)

[Key-words](#)

[Name of the disease](#)

[Name of excluded diseases](#)

[Prevalence](#)

[Diagnostic criteria](#)

[Clinical descriptions](#)

[Symptoms described by patients afflicted with MFS](#)

[Specificities of infantile MFS](#)

[MASS syndrome](#)

[Management](#)

[Etiology](#)

[Genetic counseling](#)

[Prenatal diagnosis](#)

[References](#)

## Abstract

*Marfan syndrome (MFS) is an autosomal dominant disease with an estimated prevalence of 1/5,000 individuals. Diagnostic criteria for MFS were first established in Berlin in 1986. All systems susceptible of being involved were collected, and then the major clinical signs and other minor manifestations according to the type of involvement were defined, with the presence of a certain number of clinical signs in a system establishing whether or not the individual is affected with MFS. With time, weaknesses in the Berlin criteria became evident, accentuated in particular by the development of molecular biology tests, and led de Paepe et al (1996) to revise them. At present, both sets of criteria can be used; their discriminating abilities are being evaluated. The clinical signs in MFS are mainly musculoskeletal (dolichostenomelia, arachnodactyly, joint hypermobility, spinal involvement, acetabulum protrusion, thoracic skeletal involvement), ocular (dislocated lens, axial myopia) and cardiac; this latter conditions the prognosis as a function of the severity of mitral and aortic valve anomalies. Patients with MFS should be followed by clinicians belonging to different specialties but working together within the framework of multidisciplinary consultations (cardiology, genetics, ophthalmology, pediatrics, rheumatology). Cardiovascular therapies can be proposed. MFS is a fibrillinopathy resulting from defective fibrillin-1 synthesis. The gene coding for this protein (FBN1) has been partially cloned and was localized to chromosome 15q21 in humans. At present, more than 400 mutations of the FBN1 gene have been described. A second gene implicated in MFS (called MFS2) was localized to the short arm of chromosome 3 at 3p25. This gene and the protein that it encodes are still unknown. It is currently estimated that alterations of this gene could explain 8 to 15% of the MFS cases.*

## Key-words

Autosomal dominant transmission, musculoskeletal signs, ocular features, cardiac attack, fibrillinopathy, FBN1 gene, MFS2 gene

**Name of the disease**

Marfan syndrome (MFS)

**Name of excluded diseases**

[Homocystinuria \(OMIM 236200\)](#)  
[Stickler syndrome](#) (hereditary progressive arthro-ophthalmopathy)  
[Congenital contractural arachnodactyly \(OMIM 121050\)](#)  
[Familial mitral valve prolapse \(MIM 157700 =\)](#)  
[Shprintzen-Goldberg craniosynostosis syndrome \(OMIM 182212\)](#)  
[Weill-Marchesani syndrome \(OMIM 277600, spherophakia-brachymorphia syndrome\)](#)  
[Ehler-Danlos syndrome OMIM 130060, cutis hyperelastica\)](#)

**Prevalence**

It is estimated at 1/5,000 individuals.

**Diagnostic criteria**

**1986 Berlin criteria (Beighton et al., 1988)**

The diagnosis of MFS is sometimes difficult to make: it is based on the presence of several signs in diverse systems and thus often requires the concurrence and advice of different specialties.

Diagnostic criteria for MFS were established during the 7th International Congress of Human Genetics Workshop held in Berlin in 1986 (Table 1). All systems susceptible of being involved were collected and then the major clinical signs and other minor manifestations according to the type of involvement were defined, with the presence of a certain number of clinical signs in a system establishing whether or not the individual is affected with MFS.

**Table 1. MFS diagnostic criteria established during the 7th International Congress of Human Genetics Workshop held in Berlin in 1986**

System	Major clinical signs	Minor clinical signs
Skeletal		Thoracic malformation: pectus excavatum or carinatum Dolichostenomelia not consequent to scoliosis Flat feet Arachnodactyly Spinal abnormality Scoliosis Thoracic lordosis or diminution of thoracic kyphosis Thoracic or thoracolumbar kyphosis Spondylolisthesis Exceptionally tall stature, especially compared to healthy relatives Arched palate Overgrown teeth Acetabulum protrusion Joint laxity Congenital flexion contractures Hypermobility
Ocular	Lens ectopia	Flat cornea Elongated eyeball Retinal detachment Myopia
Cardiovascular	Ascending aorta aneurysm Aortic dissection	Aortic insufficiency Mitral insufficiency due to prolapse of myxoid valve Prolapse of myxoid mitral valve Calcifications of the mitral valve Abdominal aorta aneurysm Arrhythmia Endocarditis Mitral valve prolapse without valve tissue anomaly
Pulmonary		Spontaneous pneumothorax Apical pulmonary blebs Restrictive syndrome caused by thoracic malformation Emphysema
Skin and integument		Stretch marks without obvious cause (pregnancy, marked weight loss, intense exercise) Recurrent hernias, inguinal or incisional Other hernias (umbilical or hiatal)
Central nervous system		Dural ectasia Enlarged lumbar canal and spina bifida Lumbosacral meningocele Learning disorders Hyperactivity

To make the diagnosis of MFS according to the Berlin criteria, the following signs must be found in the patient:

In the absence of a direct parent afflicted with MFS, involvement of the skeletal and at least

two other systems, with the presence of at least one major sign.

If a direct parent has MFS, involvement of at least two systems must be found. The presence of a major manifestation is desirable, but this point can be modified as a function of the family morphological type.

**Revised diagnostic criteria for MFS**

With time, weaknesses in the Berlin criteria became evident, accentuated in particular by the development of molecular biology tests, and led de Paepe *et al* (1996) to revise them (Table 2).

**Table 2. MFS diagnostic criteria according to de Paepe *et al*.**

System	Major clinical signs	Minor clinical signs	Definition of system involvement
Skeletal	Pectus carinatum or excavatum requiring surgery Upper segment (top of head to top of pubic ramus) to lower segment (top of pubic ramus to floor) or arm span to height ratio >1.05 Wrist or thumb sign Scoliosis >20° or spondylolithesis Maximal elbow extension <170° Flat feet Acetabulum protrusion	<ul style="list-style-type: none"> <li>Moderate pectus excavatum</li> <li>Joint laxity</li> <li>Arched palate with overgrown teeth</li> <li>Facies</li> </ul>	Major: presence of at least 4 major clinical signs
Ocular	Lens ectopia	Flat cornea Elongated eyeball Hypoplastic iris or ciliary muscle hypoplasia	Presence of at least 2 minor signs
Cardiovascular	Ascending aorta dilatation involving the aortic sinuses Aortic dissection	Aortic insufficiency Mitral valve prolapse with or without leakage Pulmonary artery dilatation before age 40 yr Calcifications of the mitral ring before age 40 yr Aneurysm or dissection of the abdominal aorta before age 50 year	Presence of at least 1 minor sign
Pulmonary		Spontaneous pneumothorax Apical pulmonary blebs	Presence of at least 1 minor sign
Cutaneous		Stretch marks (without pregnancy, marked weight loss) Recurrent hernias	Presence of at least 1 minor sign
Dura mater	Lumbosacral ectasia		Presence of a major sign
Genetic	A direct parent meeting diagnostic criteria Mutation of <i>FBN1</i> , known to cause MFS Presence of a genetic marker, close to <i>FBN1</i> , that is transmitted with the disease in the family		

*FBN1*: fibrillin 1 gene.

To be diagnosed with MFS, the subject being examined must have a first-degree relative afflicted with the disease, with, in addition, two systems involved with a major sign. Otherwise, in the absence of genetic criteria, the involvement of three systems, at least two with major signs.

At present, both sets of criteria can be used; their discriminating abilities are being evaluated.

**Clinical descriptions**

**Musculoskeletal involvement**

*Dolichostenomelia*

During the course of MFS, the most fundamental phenotypic anomaly is the excessive growth of the limbs (dolichostenomelia), which is further accentuated by the absence of parallel development of muscle and fat. The exterior appearance of MFS sufferers is characteristic: very tall, broad arm span, excessively thin,

deformed trunk, disproportionately long and thin fingers.

MFS victims are very tall, over 180 cm (185 ± 10 cm for our series of adult patients) for both sexes, and, children exceed the 97th percentile of height for their age. Dolichostenomelia is a fundamental clinical characteristic of MFS. Different methods of calculation can be used. The simplest and most reproducible is the arm span to height ratio. Close to 1 for the normal population, it reaches 1.03 for >80% of the individuals with MFS and becomes a major criterion when it reaches 1.05. For children and adolescents, this ratio evolves with growth. Dolichostenomelia and excessive height affect 90% of the subjects with MFS, and thus some of them can appear to be of normal height and appearance.

*Arachnodactyly*

Arachnodactyly (spider-leg like fingers) is an easily recognizable clinical expression of MFS,

demonstrated by the Walker–Murdoch thumb sign: the thumb and index finger encircle the contralateral wrist and the distal phalanges clearly overlap. Arachnodactyly of hands and feet is symmetrical but can sometimes be masked by the discrete fibrous contractures of the distal and proximal phalanges observed during MFS. Joint hypermobility and arachnodactyly give the hands of the MFS patient a highly suggestive appearance and symptomatology.

#### *Joint hypermobility*

Joint hypermobility is a common trait in MFS. The scores measured using the Beighton criteria are on the average very high (6/9 for 80% of the patients). Hypermobility of the arms is often exaggerated. The most common consequence for the feet is a valgus flat foot, often appearing early, evolving, with repercussions on the tibiotarsal and subastralgar joints.

#### *Spinal involvement*

The spinal column involvement is severe and is not comparable to the classical MFS scoliosis deformity, which is usually "double rayon", largely exceeding 20°. Its progression is reported to be more severe in children and adolescents, compared to idiopathic scolioses.

The spinal deformity of MFS is often complex. It consists of the disappearance of the dorsal kyphosis, usually giving rise to a flat back, becoming even more characteristic with the formation of an inversion of the curve with dorsal lordosis. Anomalies of the cervical spine in 104 MFS patients were recently reevaluated and compared with a control group. The following major abnormalities were found in MFS: clearly more local cervical kyphoses, asymptomatic basilar impressions (30%), atlantoaxial subluxation (56%). Enlargement of the cervical canal, as a consequence of dural dilatation and vertebral scaloping (exaggerated acquired concavity at the posterior vertebral border), seems very rare. Lumbar spondylolisthesis, generally mild, is slightly more common in the general population (18%).

#### *Acetabulum protrusion*

Acetabulum protrusion is present in 40% of MFS patients; considering only grades II and III, it is present in only 7% of healthy individuals (grade I protrusions are frequent in the general population). Acetabulum protrusion is rarely responsible for radiological coxarthrosis (3% of our serie).

#### *Thoracic skeletal involvement*

Thoracic involvement is easily recognized, giving an obviously outward (pectus carinatum) or inward deformity (pectus excavatum). These deformities can be more discrete and must be interpreted with caution; the elementary pectus

excavatum is quite common in the general population, while pectus carinatum is very rare in healthy individuals in the absence of scoliosis or previous trauma.

#### *Morphology of the head and face*

Subjects with MFS have a classical appearance of the head and face as of adolescence, with anterior–posterior axis dolichocephalia, micrognathia, malar hypoplasia. It is important to examine the mouth as it will reveal malformations characteristic of MFS: arched palate, giving at most the absence of the palatine arch and crowded teeth with evident dental malocclusion.

#### *Neuromeningeal involvement*

Strictly speaking, neuromeningeal involvement is not part of the skeletal involvement but its repercussions primarily affect the spine with lumbar scaloping, often exaggerated, and dilatation of the dural sac, sometimes massive in anatomical terms but without real clinical manifestations (see below). Dural ectasia – a major criterion – is detected by radiography alone in 40% of MFS patients (versus 5–7% of normal subjects). Systematic magnetic resonance imaging (MRI) investigations have detected dural ectasia in 92% of MFS patients, thereby reinforcing its diagnostic value for the identification of incomplete forms of the disease.

#### *Osteopenia in MFS*

The description of an elevated prevalence/frequency of fractures in children and adults with MFS led to the search for osteoporosis and/or osteopenia in these patients.

Our findings are in agreement with those reported by North American centers.

Osteopenia ( $-1 > \text{score} > 2.5$ / score ranging from  $-1$  to  $>2.5$ ) is significant/severe in MFS patients. It occurs early and equally in men and women, but was not associated with an elevated prevalence/frequency of fractures in our cohort (10%), unlike the values reported for English patients of the same age (30%). Preliminary results confirm a very precocious deficit in the acquisition of bone mass in adolescents with MFS, but its mechanism remains to be elucidated. Bone desitometry of these patients must take into consideration the highly specific morphological type (very tall, extremely thin, low body mass index) necessitating comparison of data with a control population paired at least for height.

#### **Symptoms described by patients afflicted with MFS**

The musculoskeletal involvement during the course of MFS is often restricted to the description of physical anomalies without specifying their induced morbidity, which can be

the reason for consulting. Spinal/back pain is the symptom the most frequently reported by adults (and adolescents) and the primary reason for consulting. Essentially positional and due to exhaustion, this pain is equally distributed over cervical, dorsal and lumbar segments. Pain secondary to surgical interventions for scoliosis occurs in the remaining mobile cervical and lumbar segments. The clinical repercussions of dural ectasias in MFS patients seem to be minor or non-existent in a relatively young population (mean age: 39 years). No increase lumbar or sciatic pain has been observed. In the few patients over 50 years old, aging of the lumbar spine associated with dural ectasia does not appear to have marked clinical consequences. The second most common complaint reflects the consequences of the common joint hypermobility seen in more than half the patients who experience recurrent sprains and "facile" arthralgias. Foot and ankle pain, attributed to the tibioastragal conflict, pain resulting from the extreme valgus of the hind foot and early flattening of the plantar arch represent the third main source of discomfort in adults with MFS. Adolescents and adults with MFS frequently complain (>50%) of a chronic fatigue syndrome – independent of any depressive disorder. This phenomenon, previously unreported, might arise from several sources: inadapted to the effort exerted because of the absence of a fat reserve, defective metabolic adaptation to the effects of contraction–relaxation.

### ***Pulmonary involvement***

The scoliosis and thoracic cage deformations can be responsible for a debilitating restrictive syndrome.

The frequencies of spontaneous pneumothorax and apical pulmonary blebs, which predispose to the former, are heightened.

### ***Ocular involvement***

The extent of ocular involvement conditions the functional visual prognosis of these patients because of the potential severity of lens and/or retinal disorders. The major sign of ocular involvement is a dislocated lens, which is seen in 60–80% of the patients.

#### ***Dislocated lens***

The crystalline lens is an intra-ocular transparent biconvex refractive structure whose power in the normal individuals is around 19 diopters, is located behind the iris and in front of the anterior hyaloid delimiting the vitreous body. This lens is constituted of an nucleus and a cortex contained in a capsule, which is maintained perfectly centered in relationship to the pupil by a system of suspensory ligaments, the ciliary zonule, anchored to the equator of the capsule and attached to the ciliary body and ciliary muscle. This system is of primary importance in

ocular physiology because it enables the deformation of the lens to focus clearly on nearby objects, *i.e.*, accommodation of the eye. The fibers constituting the zonule are composed of fibrillin and are thus directly affected by MFS. Thus, the progressive distension of these fibers results in lens dislocation, and can go so far as partial local (crystalline subluxation) or total rupture (crystalline luxation), which leads to the lens being displaced either into the vitreous or the anterior chamber.

Lens dislocation can occur as of birth or during adulthood and can be rapidly progressive or stable for several years. Obviously, this anatomical modification of the lens affects visual acuity, either moderately, with the appearance of a myopia index or an astigmatism easily corrected with glasses, or severely, as soon as the dislocation goes beyond the central visual axis of the eye. Finally, lens dislocation, usually into the vitreous body, is responsible for severe ocular complications, notably retinal, and can cause retinal detachment. Monitoring of the crystalline lenses in these patients is thus very important. To prevent such complications, it is possible, at the right time, to surgically remove the lens and replace it with an ocular implant to compensate for the loss of refractive power. It should be noted that this artificial lens perfectly replaces the refractive power of the native/natural one, but is unable to accommodate and thus renders the individual prematurely presbyopic.

#### ***Axial myopia***

The other common ocular anomaly in MFS is axial myopia resulting from the anterior–posterior elongation of the eyeball. This myopia exceeds –15 diopters in about 40% of the patients and –7 diopters in 10–20%. This refraction abnormality can be corrected with glasses or contact lenses, but it also predisposes the victim to sometimes severe, classical retinal complications of severe myopia. Indeed, the elongation of the eyeball occurs to the detriment of the constitutive layers of the eye, in particular the sclera and the retina, leading to dramatic thinning of these tissues with their concomitant marked fragilization. The risk of tearing and detachment of the retina is thus increased, sometimes aggravated by zonule traction in the case of crystalline subluxation.

Other ocular anomalies can be present, especially the existence of central corneal flattening, with any major effect on vision, but whose detection is informative in terms of diagnosis of forms frustes without lens dislocation.

In children, all these ocular signs can be present and the importance of monitoring the crystalline lens must be emphasized so as to intervene without delay for lens luxation, especially unilateral, in order to prevent definitive impaired vision or blindness.

**Cardiac involvement**

The extent of heart involvement condition the prognosis. Before the development of surgical procedures to replace the ascending aorta, 90% of MFS patients died of one of the cardiovascular complications of the syndrome: aortic dissection and rupture, aortic or mitral valve insufficiency progressing to cardiac insufficiency.

**Mitral valve**

The mitral valve is often redondante, with elongation of the cords and dilatation of the mitral ring. It can be responsible for mitral insufficiency that, when severe, is the main cardiac complication in young patients. But valve leakage can also appear with time and 1/4 patients with mitral valve prolapse will develop a leak during the course of their disease.

**Aortic valve**

The aortic valve leakage is almost always the consequence of ascending aorta dilatation at the level of the aortic sinus.

**Aortic anomalies**

The aortic root dilates, typically in the form of an onion. This dilatation can start in utero and its progression is difficult to predict. Two complications are to be feared. First, the aortic leakage, which can cause the modification of the positions of the valvular leaflets (because of the dilatation), depends directly on the degree of dilatation of the aortic root. Then and above all, the risk of aortic dissection or rupture must constantly be kept in mind. It increases with the increased dilatation of the aorta; the risk is small when the diameter of the aorta remains <55 mm. However, family history is important, as aortic dissections or ruptures have occurred when the aortic diameter was <50 mm. It seems that the existence of a relative who experienced aortic dissection without marked aortic dilatation predisposes to a similar event.

**Other cardiac anomalies**

The prevalence of ventricular and supraventricular arrhythmias seems to be higher in MFS patients than the general population, even in the absence of valve leakage. Rare cases of cardiac dilatation not secondary to valve leakage have been reported; they might attest to a primary anomaly of the heart muscle. Several patients with conduction disorders have also been reported.

**Specificities of infantile MFS**

The diagnosis of MFS is suggested in a child in two circumstances: the existence of a revealing symptom (skeletal, ocular or cardiac) or systematic screening of family members of an afflicted individual. The evocative symptoms during childhood are most often skeletal

(excessive height associated with scoliosis and/or a thoracic deformity) or ocular (discovery of lens dislocation); cardiac manifestations are rarely suggestive at this age.

Infantile MFS is distinguished by:

- 1) the progressive constitution of a clinical picture that becomes complete as the child ages;
- 2) the difficulty to confirm or refute the diagnosis, especially in children under 5–6 years of age;
- 3) cardiac (prevention of aortic dilatation) and skeletal management (spine, excessive height, orthodontia) closely linked to growth and puberty.

**Specificities of the clinical picture**

The clinical signs of infantile MFS are the same as those of adults. The picture is sometimes inconclusive during the first years of life, limited to simple joint laxity and arachnodactyly. As time passes, a thoracic (pectus excavatum or carinatum) and spinal deformity can appear. Stretch marks are very unusual before 7–8 years. Lens dislocation can be present as of the first years of life but can also appear only during the second decade. Cardiac involvement is variable, possible and complete as of the first year of life (mitral valve prolapse and aortic dilatation), but can also develop gradually over time.

In addition to this classical form of MFS, a neonatal form with a highly specific clinical picture is known: facial dysmorphism, arachnodactyly, neonatal contractures of the arms, possibility of a rapid evolution of the ocular (lens dislocation) and cardiac involvement (precocious mitral valve insufficiency and possibly aortic dilatation as of the first months of life).

**Diagnostic difficulties**

The progressive appearance of symptoms over time renders the diagnosis difficult to make. The Berlin criteria and, more recently, those proposed by de Paepe *et al.* do not take into consideration this possible evolution and are thus often found lacking. The same is true for certain radiological signs, such as acetabulum protrusion, very rare before 12 years or dural ectasia (major sign) whose bone manifestation seems to be evident only after 7–8 years. Thus, strict and rigorous application of these international criteria do not allow the physician to refute (familial case) or confirm (suggestive symptom) the possible diagnosis of MFS in a child. Annual monitoring and the demonstration of new clinical or radiological signs enable the diagnosis of MFS to be confirmed secondarily for some patients.

**How can the diagnosis be confirmed?**

The diagnosis is often obvious when the patient has a family history of the disease, suggestive morphology, ocular, cardiac and/or cutaneous

anomalies. It is much more difficult when the signs are less clear-cut and can be made in clinical practice only when the data can be gathered from different specialists, who are the only ones able to discern minor anomalies. To confront this difficulty, Beighton *et al.* proposed their diagnostic criteria in 1988 (Table 1). Although they achieved an international consensus, these criteria do not permit the clinician to establish the diagnosis for many incomplete forms of the syndrome. New criteria were proposed by a smaller group of clinicians who met in Ghent in 1996 (Table 2). These latter have not yet been validated and are controversial because they are too restrictive.

### **MASS syndrome**

**MASS** phenotype is the following combination of features:

**Mitral valve prolapse (MVP)** - when the mitral valve of the heart closes properly, but then flops backward allowing leakage of blood into the chamber from which it came instead of moving forward (regurgitation)

**Aortic root diameter** may be at the upper limits of normal for body size, but there is no progression to aneurysm or predisposition to dissection.

**Stretch marks** of the skin unrelated to weight gain (striae).

**Skeletal features** of the Marfan syndrome (including scoliosis, pectus excavatum or carinatum, and joint hypermobility).

It is a connective tissue disorder, which can be inherited in autosomal dominant pattern. It has been shown to result from mutations in the fibrillin gene *FBN1*. Patients with MASS phenotype never demonstrate progressive aortic enlargement or lens dislocation. While family history may be indicative, clinical follow-up is the only reliable method to distinguish MASS phenotype from emerging Marfan syndrome.

### **Management**

#### **Multidisciplinary consultations**

The diversity of the anomalies associated with MFS and related diseases make it easy to understand that these patients should be followed by clinicians belonging to different specialties but working together within the framework of multidisciplinary consultations. This approach has worked successfully for a long time in many European countries. This has not been the case in France, even though a real demand exists, as much from the doctors as patient associations. To respond to this demand, we have organized and set up the first multidisciplinary consultation for MFS at Hôpital Ambroise-Paré (in the Paris suburb of Boulogne-Billancourt in 1995). The feasibility and credibility of this project has been guaranteed by the presence in our institution of not only MFS specialists, but all the specialties relevant to MFS.

This consultation, has been open every Tuesday, from 12 noon to 7 pm, since January 1995. Patients are first met by a secretary and nurse, who help them with necessary paperwork, and coordinate the appointments with the different specialists (cardiology, genetics, ophthalmology, pediatrics, rheumatology) and the complementary examinations (electrocardiogram, echocardiography, radiographs, bone densitometry, taking of samples for genetic analyses). The overall procedure for each patient lasts between 4 and 5 hours. To assure the good care of the patient, no more than 10 subjects are scheduled for a given day of consultation. During the course of the so-called "synthesis" meetings held the Friday following the consultation, the medical records are analyzed by all the specialists cited above and a radiologist and biologist. The diagnosis is made and the therapeutic strategy defined. A consultation is then proposed to the patient to announce the results/conclusion and provide counseling as to what measures should be taken and to set up monitoring (annual or longer intervals).

Since its opening, our outpatient clinic has seen 8500 new patients (68% adults and 32% children), among whom approximately 41% come from the provinces. Analyses of the diagnoses show that 38% of the patients have a complete or incomplete form of MFS, 12% are probably afflicted (complementary examinations are ongoing) and the remaining 50% are unaffected. This last group includes relatives at risk for whom the diagnosis has been refuted and individuals with isolated skeletal signs characteristic of MFS or familial forms of aneurysm or lens ectopia. Study of the evolution of these consultations shows remarkable patient fidelity because for the year 2000 during which 366 patients (*i.e.*, 1,225 specialty consultations) were examined, 182 returned for their annual surveillance check-up. This adherence now poses another problem, which is the increased delay in seeing new patients because the latter must now wait 12 months to have an appointment. Since 1996, two other multidisciplinary consultations have been set up: one a Hôpital Robert-Debré in Paris (which accepts only children) and the other at Hôtel-Dieu in Lyon.

#### **Cardiovascular therapies available**

##### *Limitation of physical activity*

Obviously, contact sports must be avoided, competitive sports, especially if they require exertion in apnea or risk of collision. This restriction of physical activity can slow the aortic dilatation.

##### *Pharmacological treatment*

It is based on long-term administration of beta-blockers: by lowering arterial blood pressure and speed of ascension (dP/dt), they slow the

progression of aortic dilatation, independently of the aorta diameter at the time of treatment initiation. Finally, these agents lower the rate of aortic complications.

#### *Corrective cardiac surgery*

Surgery can be indicated to correct valve leakage (mitral or aortic), for severe aortic dilatation or chronic aortic dissection. Concerning the mitral valve, the redundancy of the leaflets and mitral ring dilatation are often seen, and can, like mitral prolapse, be corrected surgically. Valve sparing surgery is increasingly proposed to patients with the aim of avoiding chronic anticoagulation. Aortic surgery consists primarily of reparation of the ascending aorta with replacement of the aortic valve (Bentall operation). The risk of this procedure, when it is performed in the cold, is very low and its development has prolonged life expectancy. When the diameter of the ascending aorta exceeds 55 mm, surgery is indicated. Indeed, it is important to take into consideration not only the absolute measured diameter of aorta but also its progression over time, which can easily be obtained by regular echocardiographic monitoring. When repeated echocardiograms show abnormally rapid aortic dilatation, the risk of severe complications can indicate the need for surgery before the aortic diameter reaches the classical threshold. Finally, indications for surgery to repair aortic dissection are the same as those recommended for classical dissections, but the aortic valve is almost always replaced at the same time when the ascending aorta is involved.

#### *Pregnancy*

This is a delicate subject. The risk of aortic dissection rises during the course of pregnancy, as for the general population, especially during the peripartum period, but the literature, consisting mostly of case reports, is probably too alarmist on this subject. The experience of the John Hopkin's Hospital is more reassuring: 18 women with MFS and an aortic diameter <40 mm were able to carry their pregnancies to term. Prescription of a beta-blocker during the last trimester of pregnancy is recommended, especially if the aorta is dilated.

Musculoskeletal involvement necessitates the use of orthopedic appliances and surgery for severe scolioses. The prevalence of postural spinal/back pain is high and requires regular physical therapy. Adolescents and adults are informed of the consequences of joint hyperextensibility.

Valgus deformity of the flat foot is common and can be prevented by adapted orthopedic prostheses and corrective shoes.

## **Etiology**

### ***Pathophysiological aspects***

#### *A disease of fibrillin and the microfibrillary network*

For a long time, the primary defect responsible for MFS was attributed to components of the extracellular matrix, more specifically, collagen or elastin fibers. That hypothesis was essentially based on the histological examination of the aorta wall, which showed the classical degeneration, then fragmentation and rarefaction of elastic fibers in the media. In addition, electron microscopy also showed the disorganization of collagen fibers. However, classical biochemical analyses, subsequently complemented by genetic studies, demonstrated that these were merely alterations secondary to an unknown primary defect. This defect could be identified using two different approaches (one structural and the other genetic), which coincided and bore their fruit in the early 1990s. The structural approach provided a better characterization of the microfibrillary network of non-striated fibers of small diameter often associated with elastin but sometimes seen in isolated bundles. The major constituent of these microfibrils is a large, highly resistant protein called fibrillin. The gene coding for this protein was partially cloned and localized in humans to chromosome 15q21 in 1991. Several months earlier, the genetic approach had shown that the gene carrying the mutation responsible for MFS (MFS1) was also localized in the same region of chromosome 15. Identification of the first fibrillin mutations in suspected MFS patients (proposants) definitively demonstrated that this syndrome is a "fibrillinopathy" and not a collagenopathy.

#### *Fibrillin-1*

Fibrillin-1 is encoded by a large mRNA (approximately 10 kb) derived from a large gene (more than 200 kb), called *FBN1*, highly fragmented (65 exons and 3 alternative exons 5'). Fibrillin is a complex protein of 2,871 amino acids containing many repeat modules. Its N- and C-terminal ends and the proline-rich region have no homology with other known proteins. The central domain of the protein is formed by the repetition of several modules. Comparative analysis revealed strong homologies between 47 of these 6 cysteine-containing modules and modules of the epidermal growth factor (EGF) precursor. Forty-three of these 47 EGF-like modules also contain a conserved consensus sequence necessary for calcium binding and are thus called cb EGF-like. A second module, composed of 8 cysteines and repeated 7 times in the protein, is strongly homologous to modules described in the transforming growth factor-beta1 binding protein (TGF-beta1-BP). Finally, a third module is found twice, intercalated between the repeats of the EGF-like and TGF-beta1-BP modules. These so-called

"hybrid" modules present the characteristics of the other two previously described modules.

#### *Assembly of fibrin monomers*

Once synthesized, fibrillin monomers rapidly assemble to form microfibrils with a characteristic aspect called "pearl necklace", seen by electron microscopy. The molecular bases of this assembly remain poorly understood. Calcium certainly plays a major role, as revealed by the numerous mutations identified and which concern amino acids in cb EGF-like modules. Furthermore, calcium addition and chelation experiments showed a major impact on the organization of regions between the 'pearls'. Different models of monomer assembly have been proposed but the meaning of this association remains uncertain. Interactions between fibrillin and other constituents of the microfibrillary network also remain to be elucidated.

#### *Type 1 fibrillinopathies*

At present, more than 400 mutations of the *FBN1* gene have been described. Their analysis reveals a total absence of major rearrangements in the gene. These mutations are distributed over the entire length of the gene and the majority of them are private (only 8 cases of recurrent mutations have been reported). They are mostly mis-sense mutations leading to the replacement of one amino acid by another, and preferentially affecting cysteines. Open reading frame (ORF) shifts are seen in only 22% of the mutations, occurring equally in splicing-site and deletion mutations. These mutations result in the absence of synthesis or the synthesis of a truncated and unstable protein. In approximately 75% of the cases, the mutations are localized in a cb EGF-like module. The other mutations are found in all the other domains except the proline-rich domain (in which, to date, no mutation has been reported).

Very soon after the cloning of the *FBN1* gene, numerous studies showed that the gene mutations were associated not only with MFS (MFS), but also with different connective tissue diseases. These diseases, long considered to be collagenopathies, constitute the new group of "fibrillinopathies". This group of pathologies presents either isolated symptoms of MFS (lens dislocation, skeletal signs or aneurysm of the ascending aorta) or symptoms not belonging to the MFS spectrum (neonatal forms of MFS, Shprintzen–Goldberg syndrome, Weill–Marchesani syndrome).

#### **Genetic heterogeneity and MFS2**

In 1994, in a large French family afflicted with MFS, the implication of the *FBN1* gene could be excluded, thereby showing the existence of genetic heterogeneity. The second gene implicated in MFS (called *MFS2*) was localized

to the short arm of chromosome 3 at 3p25. This gene and the protein that it encodes are still unknown. It is currently estimated that alterations of this gene could explain 8–15% of the MFS cases.

#### *Pathogenetic mechanisms*

From a clinical point of view, MFS is characterized by a marked pleiotropism of the clinical manifestations and a wide variability of both inter- and intrafamily expression. Indeed, the ubiquitous distribution of fibrillin could explain the pleiotropism and the pathogenetic mechanisms underlying the syndrome. Hence, the abundance of microfibrillary aggregates in the ciliary zonule or elastic fibers in the aortic media enable us to easily understand how a defect of fibrillin, quantitatively the most important component of the network and probably an essential functional element, clearly explains the clinical signs and histological changes seen in MFS. As far as the variability of the interfamily expression is concerned, it is attributed to types of molecular anomalies: genetic heterogeneity (*i.e.*, implication of the *FBN1* or *MFS2* gene) and allelic heterogeneity (*i.e.*, the existence of *FBN1* gene mutations differing from one family to another).

For allelic heterogeneity, two types of mechanisms can explain the existence of moderate forms (first mechanism) or severe forms (second mechanism). In the first mechanism, the mutation leads to the synthesis of a truncated, unstable and rapidly degraded protein. Subjects carrying this type of mutation will have half the quantity of qualitatively normal fibrillin synthesized and incorporated into the extracellular matrix. The second mechanism calls upon the phenomenon of "negative dominance" and corresponds to the majority of mutations identified in the *FBN1* gene. In these patients, the mutation simply replaces one amino acid by another, leading to the synthesis of a protein that interferes with the polymerization (monomer-assembly) mechanism. The subjects carrying this type of mutation have markedly less functional fibrillin because of poor polymerization and the presence of a proteins whose structure, and, therefore, probably function are altered.

At present, no correlation between the localization of the mutation in the *FBN1* gene and one (or more) particular sign(s) has been established other than the preferential localization of mutations associated with the neonatal forms of MFS. In addition, the intrafamily variability of expression of the same mutation remains unexplained. It certainly reflects the intervention of different, still-unknown, compensating or aggravating mechanisms or genetic fingerprint phenomena (that have never been explored in this disease). These elements make it difficult to pronounce a

prognosis for MFS and considerably complicate genetic counseling.

**Contribution of biology to the diagnosis of MFS**  
Identification of fibrillin and its gene allows two types of tests, respectively, protein and molecular.

The protein test can be performed on fibroblasts obtained by culture of a simple skin biopsy. Indirect immunofluorescence with a monoclonal anti-fibrillin antibody will provide quantitative and qualitative information on the fibrillin synthesized and incorporated into the extracellular matrix produced by the cultured fibroblasts. It is also possible to conduct direct immunohistochemical labeling studies or histological examinations of the elastic network in the biopsy specimen. However, these analyses cannot confirm or refute the diagnosis of MFS, as mutated fibrillin is seen in MFS as much as in other fibrillinopathies. Nevertheless, the protein test provides substantial information in two situations: presymptomatic diagnosis or confirmation of a relative at risk (the children) and diagnosis of a hereditary fibrillinopathy that requires regular monitoring.

The most direct molecular test consists of identifying a mutation in the *FBN1* gene. But no molecular biology technique is available for routine testing that can rapidly, reliably explore such a large gene at low cost, and exploration of the entire gene is essential because, grossly speaking, each family has its own different (private) mutation. In addition, before starting such an analysis, it is important to be assured, based on a protein or genetic approach, that the individual indeed has a fibrillin mutation. The genetic strategy consists of analyzing the family with polymorphic markers of the *FBN1* gene. Its contribution is dual: confirm the implication of fibrillin and indirectly identify the mutated copy of the gene in the subject at risk. In practice, this type of study can only be done in families that are sufficiently large and have several afflicted members. The majority of families do not meet these criteria. In addition, this approach cannot be applied to sporadic cases. The contribution of biology to the diagnosis of MFS thus remains limited for the time being. Its best indication is the early diagnosis in relatives at risk. The development of new rapid molecular biology techniques associated with automation should facilitate the rapid speedy identification of mutations. In this perspective, gene analysis will become the indispensable complementary examination because it will identify with certitude the mutation carriers.

### Genetic counseling

Because MFS is an autosomal dominant disease, all the afflicted subjects must undergo genetic counseling. At that time, a detailed family pedigree, searching for signs evocative of MFS in relatives, should be established.

The first objective of the consultation is to explain to the MFS patient that he/she can be afflicted by neomutation (in which case his parents are healthy) or by the transmission of a deleterious gene (in which case one of his/her two parents has MFS). Most frequently, the disease is familial, but about 20% of the cases result from neomutation (sporadic). To determine which case is operative, a targeted examination is necessary (rheumatological work-up with skeletal radiographs, cardiological work-up with echocardiography, ophthalmological work-up with slit lamp examination of the retina) of the parent possibly having signs suggestive of the disease or the other parent when the former proves negative. If neither parent presents a priori signs evocative of the disease, they must systematically undergo a multidisciplinary examination to eliminate a *forme fruste* of the disease.

All relatives of diagnosed patients should also be screened according to the same logic. Very rarely, some families apparently escape this logic such as a family in which two healthy parents had several afflicted children. Complementary examinations demonstrated germinal mosaicism in one of the parents.

The second objective of the consultation is to explain the mode of transmission of the disease to his/her offspring, which is 1/2 because it is a dominant disease with complete penetrance. Thus, all the children (same work-up as for the parents) must be examined to detect those afflicted and to initiate monitoring and/or therapy as early as possible. Children presenting no signs of the disease should nonetheless be examined every 3 years until the age of 18 because the penetrance is not complete before adulthood.

During prenatal genetic counseling, the future parents must be informed that the degree of disease severity cannot be predicted for a child carrying a mutation, as the expression can vary from one generation to another, with the symptomatology attenuated or aggravated.

It is also important to specify to these couples that the prenatal screening is difficult to do and is only possible in certain well-defined situations (cf. prenatal diagnosis).

Finally, for the woman who has MFS with cardiac involvement, the risk of aortic dissection inherent to pregnancy must be made clear.

### Prenatal diagnosis

Prenatal diagnosis of MFS is only possible in two situations:

- 1) when the familial mutation is known (*i.e.*, it was detected in the *FBN1* gene of one of the parents)
- 2) when familial analysis of the segregation of the markers of two loci (*FBN1* and *MFS2*) enabled the identification of the gene and the

haplotype linked to the disease. N.B.: Familial analysis is not possible for sporadic forms.

In practice, the prenatal diagnosis consists of a trophoblast biopsy taken between 9 and 11 weeks of amenorrhea. The sample is sent to the molecular biology laboratory, where previous genetic studies (search for the mutation or study of markers) had been conducted. The results should be available in about 1 week.

The prenatal diagnosis remains difficult because of the extremely broad variability of clinical expression and our inability, at present, to predict the severity of the disease in a given individual. However, the diagnosis can be discussed case-by-case with couples requesting it in the framework of a genetic consultation. So far, this diagnosis has concerned only a small number of couples at risk.

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