Marfan Syndrome (MFS) — Signs and Symptoms

Marfan syndrome is caused by a disturbed production of microfibrils and leads to problems in connective tissue. It involves primarily the cardiovascular system, causing aortic dilatation and dissection. In the following sections, this article will be presenting you well-structured and concise information on the Marfan syndrome.

Definition of the Marfan Syndrome

Marfan syndrome (MFS) was first described in 1896 by Antoine Marfan, a pediatrician in Paris. Unlike many other diseases, there is the equal distribution between the genders and prevalence in all parts of the world. MFS is inherited in an autosomal dominant pattern or caused by spontaneous mutation and is about as frequent as mucoviscidosis.

The mutation is located on chromosome 15q21 (Marfan locus). This long arm of chromosome 15 includes the gene encoding for fibrillin-1. This leads to a disturbing synthesis of microfibrils and thus elastic fibers.
Pathology of the Marfan Syndrome

Marfan syndrome is an autosomal dominant disorder of the connective tissue. It affects multiple systems, e.g. the cardiovascular and skeletal systems and the eyes. It occurs in 1/5000 live births.

Marfan Traits

- Pes planus
- Crowded teeth
- Tall, thin stature
- Elongated extremities
- Flexible joints
- Pectus excavatum/carinatum
- Scoliosis

Three-body systems are mainly affected:

- Lens dislocation in Marfan syndrome with the lens being kidney-shaped and resting against the ciliary body

Ocular system (eyes): Ectopia lentis, retinal detachment.

Musculoskeletal system: dolichostenomelia (decreased upper: lower segment ratio), Arachnodactyly, thoracic cage deformities.

Cardiovascular system (heart/aorta): aortic dissection, mitral valve insufficiency.

The degree of the manifestations varies to a high extent! The main cause of death, aortic dissection, is, however, often not detected. Typical manifestations of neonatal MFS are, in addition to those mentioned above, dolichocephaly, malar hypoplasia, enophthalmos, retrognathia and an impaired range of motion of peripheral joints.

Genetics of the Marfan syndrome

- Mutation in FBN 1 gene on chromosomes which encodes fibrillin-1
- 75% of patients with MFS have affected parents
- 25% de novo mutation

Skeletal abnormalities

- Tall stature
- Long headed
- Arachnodactyly (long thin digits)
- Hyperextensible joints
- High arched palate
- Scoliosis, kyphosis, slipping off vertebrae
- Pectus excavatum

**Ocular changes**

- **Ectopia lentis**: Dislocation of the lenses
- Myopi
- Retinal detachment
- Early glaucoma
- Early cataract

**Cardiovascular lesions**

- **Cardiovascular symptoms are the main cause of morbidity and mortality**
  - Degeneration of the tunica media
  - Dilated, incompetent aortic root with valvular incompetence
  - Mitral valve prolapse and regurgitation
  - Aortic aneurysms may dissect or rupture
  - **Monitoring by echocardiography is required!**

**Neurological lesions**

60% of the patients who have Marfan syndrome are known to have dural ectasia.

**Diagnosis of the Marfan Syndrome and Ghent Nosology**

Ghent nosology was introduced in 1996 and has made a diagnosis of MFS easier worldwide by resuming all diagnostic criteria. If the family history is negative, three major criteria in two different body systems must be present and a third system has to be involved. **It was revised in 2010. There are seven new criteria that lead to a diagnosis.**

**In the absence of a family history of MFS:**

1. Aortic root Z-score ≥ 2 AND ectopia lentis
2. Aortic root Z-score ≥ 2 AND an FBN1 mutation
3. Aortic root Z-score ≥ 2 AND a systemic score > 7 points
4. Ectopia lentis AND FBN1 mutation with known aortic pathology

**In the presence of a family history of MFS:**

1. Ectopia lentis
2. Systemic score ≥ 7
3. Aortic root Z-score ≥ 2

**Points for systemic score:**

- Aortic aneurysm
- Mitral valve prolapse
- Pectus excavatum
- Pulmonary stenosis
- Mild myopia
- Scoliosis
- Tourette syndrome
- Cystic fibrosis
- Arterial aneurysm
- Renal cysts
- Marfanoid habitus
- Aortic dissection
- Cardiac conduction defects
- Retinal detachment
- Acroosteolysis
- Diastolic murmur
- Pulmonary hypertension
- Renal stones
- Ocular changes
- Cardiovascular symptoms
Wrist AND thumb sign = 3 (wrist OR thumb sign = 1)

- Pectus carinatum deformity = 2 (pectus excavatum or chest asymmetry = 1)
- Hindfoot deformity = 2 (plain pes planus = 1)
- Dural ectasia = 2
- Protrusio acetabuli = 2
- Pneumothorax = 2
- Reduced upper segment/lower segment ratio AND increased arm/height AND no severe scoliosis = 1
- Scoliosis or thoracolumbar kyphosis = 1
- Reduced elbow extension = 1
- Facial features (3/5) = 1 (dolichocephaly, enophthalmos, down-slanting palpebral fissures, malar hypoplasia, retrognathia)
- Skin striae (stretch marks) = 1
- Myopia > 3 diopters = 1
- Mitral valve prolapse ¼ 1

Systemic participation is available when 7 or more points are reached.

**Treatment of Marfan Syndrome**

Patients can only be treated individually for symptomatic management, but the most important part is to have regular appointments with ophthalmologists, cardiologists, and orthopedic specialists, as they treat the systems that are mainly affected. It is crucial to monitor the aortic root diameter being assessed echocardiographically. Prospective and
retrospective trials have shown that propanol and atenolol can slow down aortic dilatation, resulting in increased usage of beta-blockers. This also helps prevent or forgo necessary cardiac surgery.

Life expectancy for patients with MFS has increased in the past few years. This is mainly attributed to cardiac surgery that patients undergo soon after the diagnosis to prevent rupture and dissection of the aorta.

Multidisciplinary Therapy

- Cardiology, genetics, ophthalmology, orthopedics, cardiothoracic surgery
- Follow with echo
- **Beta-blockers**
  - Angiotensin II inhibitors/transforming growth factor-beta inhibitors
  - Strict blood pressure control
  - Aortic graft for aortic dilation > 5 cm
  - Avoid caffeine, stimulants, heavy exercise
  - Treat scoliosis

Prognosis

The vital factors in the management of MFS are:

- Diagnosis
- Monitoring of aortic aneurysm and cardiac valves.
- Cardiovascular surgical intervention when the aortic root area/body height ratio becomes abnormal.
- Early diagnosis and surgical management of acute aortic dissection.
- Beta-blocker control and surgery when indicated.

Complications

**During Pregnancy** - Aortic dissection or rupture may occur when the aortic diameter becomes abnormal. A multidisciplinary approach is recommended.

**Pulmonary** - Pneumothorax may occur. Lung expansion may be restricted due to pectus excavatum or scoliosis. MFS increases the risk of sleep apnea.

**Orthodontic** - Maxillary narrowing resulting in the high-vaulted palate and mandibular retrognathia resulting in malocclusion is the most common features.

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