# Disorders of the Connective Tissue

# 26

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## 26.1 Marfan's Syndrome

The term Marfan's syndrome (MFS) indicates a connective tissue disorder which causes skin, ocular, skeletal, and cardiovascular abnormalities.

The first description of the marfanoid habitus was made by Prof. A.B.J. Marfan [1] in 1896, when, at a meeting of the Société Médicale des Hopitaux de Paris, he reported the case of a 5-year-old girl with asthenic physical conformation and excessive length of limbs, fingers, and toes (spider's legs, arachnodactyly).

In a clinical update, published on ***Circulation*** in 2005, Milewicz et al. [2] define MFS as a hereditary disorder of the connective tissue with a prevalence of about 1 in 3000–5000 individuals. The syndrome is due to a mutation in the FBN-1 gene, located in chromosome 15 and encoding for fibrillin-1, a glycoprotein which is a major component of the extracellular matrix fibrils [3, 4].

The largely known life-threatening complication of this syndrome is represented by the progressive enlargement of the ascending aorta, leading to aortic regurgitation, aneurysm, and rupture. In past times, this complication implied a life expectancy no longer than 45 years in the majority of the patients [5]; according to McCusick [6], less than 10% of MFS patients lived more than 40 years. In about 75% of the cases, MFS is inherited according to an autosomal dominant pathway with complete penetration and variable phenotypic expression [2]; in about 25% of the cases, the mutation is sporadic. The diagnosis is based mainly on clinical findings, the so-called Ghent criteria [7, 8].

Renal cysts are not included into the diagnostic parameters; however, familial co-occurrence of MFS and adult polycystic kidney disease, due to a mutation in the PKD-1 gene located in chromosome 16 [9], has been reported [10]. This kidney disease has been found to be associated with vascular abnormalities, in particular with abdominal aortic aneurysms [11].

As the most common, and most life-threatening, manifestation of MFS is the involvement of the aortic root and ascending aorta, the current follow-up protocol is based on the systematic investigation of the heart and thoracic aorta [12]. However, after a number of case reports regarding aneurysms of the abdominal aorta and peripheral arteries and the extended life expectancy in MFS patients due to the remarkable results of cardiovascular surgery, attention is being focused on aneurysms outside the thoracic aorta in young, young adult, and adult patients.

In 2011, Yetman et al. [13] reported the study of 140 adult (>18 years) patients, after ruling out the possibility of Loeys–Dietz syndrome [14] through the specific genetic testing for mutation

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**Table 26.1** Popliteal artery aneurysm in Marfan's syndrome

| Author, year | Patient | Symptoms | Treatment, outcome |
|---|---|---|---|
| Wolfgarten [22], 2001 | M, 37 years | None[a] | Dacron graft, ok 1 year |
| Al-Hakim [45], 2003 | M, 50 years[b] | Local pain | Resection (?) + vein graft, ok 9 years |
| | M, 55 years[b] | None | Resection (?) + vein graft, ok 4 years |
| Tijani [23], 2012 | M, 49 years[c] | ? | Left: partial resection + femoro-popliteal vein bypass. At 9 years, distal anastomotic aneurysm and occlusion; repeated fibrinolysis and extension of the bypass to the tibioperoneal trunk |
| | M, 49 years[c] | ? | Right: partial resection and femoro-tibioperoneal vein bypass; ok (?) 9 years |
| Gaertner [15], 2014[d] | ? | | |

[a]Associated abdominal aortic aneurysm
[b]Same patient, affected with autosomal dominant polycystic kidney disease, marfanoid habitus
[c]Same patient, with bilateral popliteal aneurysm; when 46-year-old operated for abdominal aortic aneurysm
[d]Ultrasound diagnosis (see text)
?Data are not well reported

of TGFBR1/TGFBR2; about one-third of the patients presented aneurysms involving the abdominal aorta and/or peripheral arteries. This finding offered some degree of correlation with prior aortic surgery and the presence of risk factors like smoking. The authors concluded that surveillance also of distal aorta and peripheral arteries is warranted in adult MFS patients. In 2014, Gaertner et al. [15] corroborated this statement through a meticulous ultrasound study of 15 MFS patients aged 27–44 years: they found that 10 (67%) presented aneurysms outside the thoraco-abdominal aorta (three iliac, one femoral, one popliteal, one brachiocephalic, two subclavian, two vertebral, one renal).

Aneurysms of the abdominal aorta may be associated with aneurysm of the thoracic aorta [16, 17] and are not frequent, representing about 10% with respect to thoracic aortic aneurysms, according to Takayama et al. [18], who reported six cases. However, they may be isolated [19]. Lafferty et al. [20] described a ruptured abdominal aortic aneurysm; in 1982, Roberts and Honig [21] were able to find only eight cases of fusiform abdominal aortic aneurysm reviewing the English language literature from 1951. The association with popliteal aneurysm was the object of case reports [22, 23].

Subclavian aneurysms [24, 25] seem to be treated effectively through endovascular procedures [26]. A case of bilateral axillary aneurysm in siblings was reported by Saito et al. [27]. In 2006, Nguyen et al. [28] described a case of ulnar artery aneurysm.

Aneurysmal disease of extracranial cervical arteries has been reported repeatedly [29–32]. The occurrence of aneurysms of the intracranial carotid artery [33, 34] is contested by Conway et al. [35]

Aneurysms of the iliac arteries are not rare [36–38], occasionally ruptured [39]. Rupture followed sport activity in the case reported by Aschwanden et al. [40]; in the case report by Mounier-Behier et al. [41], a dissecting iliac aneurysm was the first clinical sign of MFS. Recently, gratifying results with the treatment of iliac aneurysms in MFS by stent grafting with the sandwich technique have been reported [42, 43].

Aneurysms of the femoral artery are very rare, one case being described by Hatrick et al. [44].

In Table 26.1, the cases of popliteal aneurysm are outlined.

## 26.2 Ehlers–Danlos Syndrome

Under the name of Ehlers–Danlos syndrome (EDS), several heritable disorders of the connective tissue are comprised, classically manifesting, from the clinical point of view, through skin hyperextensibility, joint hypermobility, and tissue friability.

The eponym pays a tribute to the accurate clinical observations and descriptions by

E. Ehlers [46] in 1901 and H.A. Danlos [47] in 1908. However, typical "EDS" cases had been reported, in 1892, by Tschernogobow [48] and, already in 1682, the Belgian surgeon Van Meekren [49] illustrated, on the front cover of his book ***Observationes medico-chirurgicae***, a young man with exceptional elasticity of the skin (de extraordinaria dilatabilitate cutis) (Fig. 26.1).

Several types of EDS were recognized through the years, amounting to eleven or more, following a Roman numeral list. This classification was ruled and simplified through the so-called Villefranche nosology [50]: from 1997 six types of EDS are recognized, identified with a descriptive method. The former type IV EDS is now called vascular EDS, characterized by an impres-


**Fig. 26.1** Young Spanish man with skin hyperelasticity (from Van Meekren [49])

sive incidence of heavy arterial complications and as well, but in a less catastrophic way, by rupture of the intestine and of the gravid uterus.

Owing to these life-threatening complications, type IV EDS focused particular attention by clinicians, deserving the private eponym of Sack–Barabas syndrome, from the work of G. Sack [51] (credited for having described in 1936 the first case of vascular EDS) and of A.P. Barabas [52, 53] (who gave the appellative of arterial to type IV EDS and reported five cases, of which one with fatal aortic rupture). Barabas' cases enlightened some of the complications of the disease: tears of major arteries, aortic rupture, arteriovenous fistulae, varicose veins.

In general, even after Villefranche, the appellative type IV EDS continues being used, together with those of arterial, vascular, or ecchymotic [54].

Vascular EDS is caused by a heterozygote mutation of the gene COL3A1, located in chromosome 2, encoding for type III collagen; the mutation is transmitted by autosomal dominant trait [55]; several molecular mechanisms have been described and most mutations are unique for each family, without any correlation between genotype and phenotype [56]. The striking decrease in the production of collagen III was demonstrated by Pope [57]; Cikrit et al. [58], reporting on two families with EDS IV, observed that only 5–10% of skin fibroblasts in tissue culture produced collagen III, instead of the normal 40% or more. The prevalence of EDS is estimated as 1/5000–1/25,000 [59, 60] and type IV represents only 4–5% of all cases. The defect in collagen III production results in marked vessel fragility leading to aneurysm, arteriovenous fistula, arterial dissection, and spontaneous arterial rupture [61].

Clinical diagnosis of vascular EDS relies on four main features [55, 56, 62]:

- Extensive and easy bruising, frequent ecchymoses and hematomas.
- The skin is thin and translucent, with visible veins; it is very fragile; scarring processes are abnormally prolonged, ending into enlarged scars with the aspect of cigarette paper [63].
- Acrogeria: premature aging of the skin of extremities; this implies also a characteristic facial feature (emaciated face, sunken cheeks, nose thin and pinched, thin lips).
- Ruptures of arteries, intestine, gravid uterus.

Skin hyperelasticity and joint hypermobility are uncommon [64], the latter being observed almost exclusively at fingers level.

Also in cases with marked phenotypic expression, diagnosis may be difficult, owing to the rarity of the disease and to the possibility of sporadic mutations, which exclude the support of a significant family anamnesis [61]. Many patients are totally unaware of their condition until a catastrophic event (vascular or visceral rupture) manifests. Median survival is 48 years [55]. Of the 31 patients collected at the Mayo Clinic from 1971 through 2001 [65], only 11 were alive at the age of 40 and 5 at the age of 60. In the same series, survival free of any complication was 84% by the age of 20 and 37% by the age of 40; survival free of vascular complications was 39% by the age of 40 and 20% by the age of 60. In the review of Pepin et al. [55], the cause of premature death of 131 patients was arterial dissection or rupture in 109 (78%) with 78 cases of rupture of the thoracic/abdominal aorta and nine cases of cerebral hemorrhage. In the series collected by Cikrit et al. [66], aortic rupture was the cause of death in 9/33 (39%). The risk of significant complications [55] was 25% by the age of 20 and more than 80% by the age of 40: of 136 patients surviving after the first complication, 52 (38%) encountered a second complication.

Arterial complications consist often on ruptures and pseudoaneurysms, but also true aneurysms are observed [65]. Cikrit et al. [66] were able to collect, in the English language literature from 1956 through 1983, 31 cases with spontaneous arterial perforation and/or aneurysmal disease, adding five personal cases: the episodes of spontaneous hemorrhage were 41, of which eight from the aorta and ten from the popliteal artery or its trifurcation; dissections and aneurysms were 28, none involving the popliteal artery. In a series (2000–2010), mainly focused on non-emergency

cases, of 26 vascular EDS patients from Johns Hopkins [67], imaging studies revealed 41 aneurysms, 21 dissections, 2 stenoses, without any mention of popliteal artery involvement.

Vascular complications are also observed in the classic forms of EDS [68], both in the former type I or gravis [69] and in the type II or mitis [70, 71].

The vascular event may be the first sign of the disease [72] in as much as 80% of the cases [66]. The lack of a preoperative diagnosis of the basic disease adds to the task of the surgeon, unaware of the peculiar conditions of the vessels, and tissues in general, which he is going to handle. The more catastrophic vascular complication is represented by abrupt and life-threatening hemorrhage, deriving from a dissection or aneurysm but, very often, by an apparently normal artery. The so-called spontaneous rupture is a frequent cause of death when the brain or thoracic/abdominal cavities are involved; it represents a serious condition also when located in a limb artery, due to the very difficult management of the ruptured vessel.

Spontaneous rupture depends on the extreme fragility of the arterial wall. Sometimes a traumatic event precedes the rupture, representing an occasional and precipitating causative factor. Trauma may be relevant and not belonging to daily life activities: rupture of the splenic artery while dancing French cancan [53]; avulsion of the subclavian artery during a match of basket [73]; aortic rupture after going slide into a swimming pool and hitting the water with the abdomen [74]. However, most of these traumas are really of minor entity and would be innocuous in a normal person: rupture of the popliteal artery after an erroneous movement after turning in bed [73]; popliteal artery rupture in a 13-year-old girl after jumping up and down [75]; iliac artery rupture after lifting a small room air conditioner [66]; rupture of the thoracic aorta while cycling [76]; avulsion of the thoraco-dorsal artery after gymnastic at school [76]; rupture of the iliac artery after cycling [77]. Among limb arteries, the popliteal artery and its trifurcation look particularly at risk [66, 78]: Wright et al. [75] emphasized the role of tourniquet, in a case of popliteal artery rupture, to manage the artery in conditions of no-flow, no-pressure.

In the exhaustive review published in 2013, Bergqvist et al. [61] analyzed 231 patients, recording 93 aneurysms, 28 dissections, and 75 non-aneurysmal arterial ruptures. Of the 93 aneurysms, 16 were aortic, none popliteal. In general, reviewing the literature, it is evident that EDS IV aneurysms may affect any large- or medium-size artery: aorta [74, 79–82]; subclavian [63]; intracranial arteries [83, 84]; carotid and vertebral [85, 86]; iliac [87]; femoral [85, 88]; infrapopliteal arteries [89, 90]. In 1996, Freeman et al. [91] reviewed 17 patients with several aneurysms (12 aortic, 2 subclavian, 4 carotid, 1 vertebral, 1 hepatic, 1 of the superior mesenteric artery). In 2000, Parfitt et al. [92] reported a series of visceral aneurysms: three splenic, three hepatic, three renal (bilateral in two patients), two coeliac, two of the superior mesenteric artery.

Arteriovenous fistulae are frequently reported, assuming particular relevance when involving the internal carotid and the cavernous sinus [83].

Aneurysms of the popliteal artery are very rare. Stella et al. [81] report the angiographic finding of bilateral dilation of the popliteal artery in a case of multiple aneurysms. Zilocchi et al. [93], reviewing the imaging studies of 28 patients (Mayo Clinic, 1971–2006), observed anomalies of the femoro-popliteal tract in three patients and ascertained the presence of a popliteal aneurysm, together with a femoral aneurysm, in a 50-year-old male patient.

Several patients affected with vascular EDS experience different and multiple arterial complications in the course of their life. Bellenot et al. [94] treated, during a 9-month period, the successive ruptures of left iliac, right iliac and hepatic arteries in a 25-year-old male patient. Grundtner et al. [82] performed more than ten open and endovascular procedures to extend the life of a patient from 11 to 27 years when he succumbed to the rupture of a previously ligated splenic artery aneurysm.

Treatment of arterial lesions of EDS IV is difficult and often unrewarding. Diagnostic angiog-

raphy is a dangerous procedure owing to the heavy complications consequent to arterial puncture and as well, and more important, to the damage from inside procured by guide-wires, catheters, and injection pressure. After the initial warning [95], a complication rate of 16–67% and a mortality of 6–19% were put into evidence [66, 91]. Angio-CT and angio-RM are currently the recommended diagnostic methods. The surgeon, often without any knowledge about the condition of the patient, finds very fragile vessels: handling and suturing are demanding and frequently disappointing. Vascular clamps, even if padded, can result in arterial transection [76, 96–98]. Blood vessel walls have a wet-tissue or blotting-paper consistency and fail to hold sutures [63, 99, 100]. The key to be successful in such operations [97] relies on the preoperative diagnosis of EDS and the use of a surgical technique ad hoc: by general consensus, try to avoid clamps and to achieve hemostasis by balloon occlusion; to use interrupted sutures reinforced with Teflon pledgets; to obtain final hemostasis with glues and prolonged compression. Whenever possible, ligation should be preferred to reconstructive procedures [63, 66, 75, 101], performing avoiding trauma too close to vessels by using umbilical tape-like material or interposing a strip of synthetic graft between the vessel and the ligature.

Successful reconstructive procedures are seldom reported [66, 72, 77, 80–82] and a diffuse opinion is that surgery should be performed only in the emergency setting and only in real life- (or limb-) threatening situations [92]; hemodynamically stable patients with arterial rupture should be managed conservatively, through immobility in bed, compression, and blood transfusions [101]. Bergqvist et al. [61] seem to attribute to this conservative attitude the reduction in mortality from 50% to 39% between two series of patients, 112 up to 1996 and 119 after 1996. Opinions, however, are not uniform. Two very important reports were aired, one from Mayo Clinic [65] and the other from Johns Hopkins [102]. The former includes only vascular EDS patients and agrees with the abovementioned tendency: 15 patients were submitted to open or endovascular procedures and of these 70% were performed in emergency. The latter relies on 40 patients submitted, almost exclusively in election, to open or endovascular treatment for vascular complications of EDS (classical type 15, hypermobile 16, vascular 9). Operations on vascular EDS patients were performed for aortic involvement and a mortality of 22% (2/9) was observed. The authors conclude that elective procedures should be privileged, to avoid the rather disappointing results of emergency procedures.

Endovascular procedures in EDS IV have been performed on several occasions to achieve occlusion of a bleeding artery [103] or of a visceral aneurysm [104, 105]. Consensus exists on the effectiveness of embolization procedures when feasible [65, 102] and of balloon occlusion of carotid-cavernous fistulae [106]. All these procedures are obviously exposed to dangers analogue (and enhanced) to those of catheter angiography, sometimes with catastrophic evolution [107]. Stent-grafting of an aortic aneurysm (patient with classic or type I EDS) has been successfully performed [101] and applied also on visceral [108] and peripheral arteries [82, 87, 109]. However, stent-grafting looks to be not strongly recommended, due to the risk of perforation and erosion at the fixation zone and the high incidence of reinterventions [110, 111]; apart the risks inherent to endovascular manipulations, large-bore tools, large angio-accesses. In the 1996–2010 review by Bergqvist et al. [61], mortality was 30% (13/44) after open procedures and 24% (8/33) after endovascular treatment.

Finally, it must be mentioned that Celiprolol (ß-1-adrenergic antagonist and ß-2-adrenergic agonist) has been used in a randomized trial [112], demonstrating, during a mean follow-up of 47 months, a significant ability to reduce the occurrence of arterial dissection/rupture in vascular EDS patients.

## 26.3 Loeys–Dietz Syndrome

Loeys–Dietz syndrome (LDS) is a rare autosomal dominant disorder causing a diffuse disease of the connective tissue and predisposing individuals to aortic and arterial aneurysms [113].

Loeys et al. [14] described the syndrome in 2005, identifying its genetic origin in a mutation of the TGF-ß receptor; after one year [114] they published an exhaustive clinical report, relying on 52 families and 90 patients. The disease was characterized by a triad of signs: arterial tortuosity and aneurysms, hypertelorism, bifid uvula or cleft palate; about 25% of the families presented the phenotype of vascular Ehlers–Danlos syndrome, which was ruled out by studies of the type III collagen. In this early series, median survival was 37 years; 27 patients died at the mean age of 26, and the most common cause of death was thoracic or abdominal aorta dissection (89%), followed by intracerebral bleeding (7%).

Ritelli et al. [115], reviewing the current knowledge about this syndrome, recognize four types, all deriving from mutations in genes of the TGF-ß signaling pathway. LDS1 and LDS2 patients are prone to major vascular events and have a short life expectancy [116]; they frequently present cutaneous signs similar to those observed in the Ehlers–Danlos syndrome. LDS3 patients too present important vascular manifestations, together with skeletal deformities and, frequently, osteo-arthritis at a young age [117]. In LDS4 patients, the vascular phenotype looks less aggressive and less life-threatening; aortic aneurysms and dissections are less frequent and manifest later [115].

Surgical and/or endovascular treatment of aneurysms in LDS patients, in the light of the still scarce experience so far gained, appears gratifying [118–120] especially when the results are compared with those obtained in Ehlers–Danlos syndrome. A careful surveillance of the patient and an aggressive attitude toward new successive vascular events can assure prolonged and satisfactory life as demonstrated by Beckman et al. [121]: a man, initially treated at the age of 38 for an aortic dissection Stanford type A, was still alive and actively working 25 years later, after repeated treatments for involvement of thoracic and abdominal aorta and of iliac, femoral, carotid, and subclavian arteries. Reporting in 2015 the experience at Duke University Hospital, in Durham, Williams et al. [122] observed that 10 out of 11 patients surgically treated were alive after a mean follow-up of 60 months (8.4–172); the patients were aged 20–58 years when first treated by the Duke team, and 7 of them had already been submitted to surgery elsewhere.

**Table 26.2** Popliteal artery aneurysm in Loeys–Dietz syndrome

| Author, year | Patient | Clinical picture |
|---|---|---|
| Johnson [127], 2007 | M, 55 years | Bilateral popliteal aneurysm + aortic root dilation + aneurysm of sup. mesent. artery[a] |
| Stephenson [128], 2012 | M, 28 years | Bilateral popliteal aneurysm (previous aortic dissection)[b] |
| Kuma [125], 2015 | M, 29 years | Bilateral popliteal aneurysm + several peripheral aneurysms[c] |

[a]Right aneurysm (larger) repaired
[b]Resection + PTFE graft
[c]First aneurysm treated at 24 years with vein graft; graft dilation observed at 26 years; at 29 years, substitution of the aneurysmatic vein graft with PTFE and diagnosis of several peripheral aneurysms, of which one popliteal contralateral

Involvement of peripheral arteries is not frequent [123], but the rarity of reports [119, 124] could derive from the prevailing clinical role of aortic dissections and aneurysms [125]. A review of the literature allowed to find three cases of popliteal aneurysms (Table 26.2), all treated with apparent good result. In one case [125] vein grafting was complicated by aneurysmal dilation of the graft, which was substituted with a PTFE prosthesis; microscopically, the graft showed "diffuse fragmentation and loss of the elastic fibers with an increase of proteoglycan material that formed pools between the remaining elastic lamellae." This picture was similar to that observed in arterial specimens obtained in LDS patients; the dilation would recognize, according to this finding, the same underlying pathology of arterial disease. Similarly, aneurysms in vein grafts used in the treatment of atherosclerotic disease are attributed to atherosclerotic involvement [126].

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