Neurofibromatosis

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Neurofibromatosis (NF) was described in 1882 by von Recklinghausen [1]. The clinical characteristic of this disease is heterogeneity [2]. Several types of NF have been identified [3], of which NF-1 is the most common. NF-1 is considered as corresponding with von Recklinghausen's disease [4].

NF-1 is caused by a mutation of a gene located in the long arm of chromosome 17, encoding the protein neurofibromin [5, 6], which is a negative regulator of the Ras oncogene signal transduction pathway [7]. The mutant gene is transmitted with an autosomal dominant pattern of inheritance; however, in about half of the cases of NF-1 the mutation is spontaneous [8].

Common and largely known signs of the disease are: multiple neurofibromas, café-au-lait spots, iris hamartomas (Lisch nodules); less frequently, but not rarely, learning disabilities, skeletal abnormalities, axillary and inguinal freckling. Life expectancy in NF-1 patients is reduced, owing to two types of complication [9, 10]: propensity to connective-soft tissue tumors and vascular involvement. Tumors observed in NF-1 patients include acoustic neuroma, meningioma, neurofibrosarcoma, astrocytoma, glioblastoma, malignant schwannoma, and pheochromocytoma. Regarding the latter, according to some authors [11, 12], 5–25% of the cases are encountered in NF-1 patients; however, Brasfield and Das Gupta [13] reported only one case in a series of 130 patients. In 1981, Riccardi [3] observed that cerebral tumoral lesions represented the cause of death in more than 70% of the cases.

Vascular involvement in NF was described by Reubi [14] in 1944. Thereafter, vascular lesions (stenoses, aneurysms, AV malformations) have been observed with the frequency of 0.4–6.4% [15], representing a well-recognized albeit rare pathology [16–20]. Despite its rarity, vascular involvement bears a relevant clinical importance, as a cause of renovascular hypertension in children and young adults [4, 16, 20, 21] or of dramatic and sometimes fatal hemorrhages from arterial disruption.

The term vascular neurofibromatosis was coined by Feyrter [22] in 1949; 44 cases were collected in 1959 by Khalatbari [23]; the term is currently accepted by geneticists [24, 25] to indicate those cases of NF-1 in which vascular lesions play an important role in the clinical presentation. Practically, every artery may be affected [26], including intracerebral [27–29] and pulmonary [30] arteries, mainly under the form of stenosing lesions but also of aneurysmal lesions of the epiaortic trunks [31, 32], thoracic or abdominal aorta [4, 31], intracranial vessels [17, 33], renal arteries [18, 34, 35], and visceral arteries [26, 36]. And these aneurysms, like any aneurysm,

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A. Cavallaro (ed.), *Aneurysms of the popliteal artery*,
https://doi.org/10.1007/978-3-030-49687-6_24

are subjected to progressive dilation and rupture [31]. Veins too may be involved [4, 37].

The real incidence of aneurysms is not known, because of the clinical inaccessibility of many silent lesions, and probably the incidence of vascular lesions, in general, is underestimated. Reubi [14, 38] suggested that vascular lesions, if carefully searched for, might be found in any case of NF. In a series of autopsies of NF-1 patients died for other causes [39], vascular abnormalities were found in 7/18 (39%). According to Fienmann and Yakovac [40], vascular involvement is present in about 10% of the cases.

Detailed studies of the vessel alterations in NF were accomplished by Reubi [14, 38] on arteries of diameter up to 1 mm, and continued by Feyrter [22] and by Ratzenhofer [41], resulting six types of lesion, sometimes reciprocally overlapping: pure intimal, advanced intimal, nodular-aneurysmatic, periarterial nodular, epithelioid-cell type, pericapillary-interstitial.

Lesions are apparently different in small-size and in large-size arteries, and this could represent the complex nature of the disease which affects tissues of neural crest and mesodermal origin [42]. According to Salyer and Salyer [39], proliferation of Schwann cells within the arterial wall is the common pathogenetic basis, even if, in small vessels, mesodermal dysplasia, expression of secondary degenerative changes, dominate the microscopy picture. Many authors, however, believe that two different pathogenetic mechanisms are present. In small- and medium-sized arteries, intimal proliferation of spindle cells, probably originating from smooth muscle cells [43] takes place with secondary degeneration of the muscular and elastic components of the media, leading either to occlusion of the lumen or aneurysm; this process might be the cause of aneurysm also in larger arteries like the common carotid [44]. In general, however, in large arteries, the process would be different, consisting on the invasion and weakening of the arterial wall by neurofibromatous or ganglioneuromatous tissue [31, 37, 45], representing the involvement of adventitial nerve fibers in the generalized disease. This dual type of pathological process was outlined by Greene et al. [19] in 1974:

- Larger arteries: invasion by Schwann cells, with intimal thickening and destruction of the media, leading to either stenosis or saccular aneurysm
- Smaller arteries: mesodermal dysplasia causing a proliferation of smooth muscle cells in the intima resulting in stenosing lesions and occasionally post-stenotic aneurysms

A third mechanism, quite different, is occasionally represented by the invasion of the arterial wall by adjacent neurofibroma [46].

Reviewing the Mayo Clinic experience (1976–2005), Oderich et al. [4] report 31 cases of NF-1 vasculopathy (15 with positive family history): invasion by neural tumor was present in 4 patients; 18 patients presented 40 aneurysmal lesions and 7 presented 20 stenosing lesions. Microscopy, when available, was often consistent with fibromuscular dysplasia with a predominance of intimal thickening; in five patients (aged 3–32 years) arterial invasion by Schwann cells could be demonstrated; two aortic aneurysms, in older patients, were frankly atherosclerotic. This relevant study enlightened two problems inherent to NF vascular disease:

- Lesions are often multiple, as repeatedly encountered in other reports [18, 26, 34, 45, 47].
- Should all vascular lesions observed in NF patients be classified as expression of NF vasculopathy? Probably, a high degree of prudence is necessary, especially in older individuals and if a microscopy support is lacking.

Arterial involvement in NF-1 is a rare condition, and particularly infrequent are lesions of peripheral arteries: Lin et al. [24] found only 16 cases out of 2322 patients. Aneurysm and/or pseudoaneurysms of epiaortic and limb arteries, owing to their rarity and also to the frequently dramatic presentation, have been the object of several case reports appeared during the last 25 years. An exhaustive review of the English-language literature was summarized by Oderich et al. [4]. A short survey of some cases is now reported, just to give an idea of the entity of the

problem and as well of the trend in the therapeutic approach. Three ruptured subclavian artery aneurysms were successfully treated, one by ligature and cross-over by-pass [48] and two by endovascular therapy [49, 50]. Surgical treatment was successful in two cases of brachial artery involvement [44, 51] while it was followed by patient's death in two other cases [52, 53]. Scheuerlein et al. [54] reported a good result with endovascular treatment of a ruptured ulnar artery aneurysm. Rupture of vertebral artery aneurysm was treated successfully in one case [55] with endovascular coil occlusion; in another case with intrathoracic rupture and hemothorax [56], the patient died. Internal carotid aneurysms were treated with good result either by resection and vein grafting [57] or by endovascular stenting [58, 59]. A ruptured aneurysm of the deep femoral artery was simply ligated [60], while in a similar lesion affecting the superficial femoral artery, exclusion and Dacron grafting were successfully performed [61]. An aneurysm of the anterior tibial artery was simply resected [62].

In Table 24.1 are summarized the cases of popliteal artery aneurysm in NF-1 patients as resulting from literature.

Table 24.1 Popliteal artery aneurysm in NF-1 patients

Author, year	Clinical data	Treatment
Huffman [63], 1996	Male, 58 years, symptomatic	Exclusion and vein by-pass
Ilgit [64], 1999	Female, 11 years, thrombosed	Amputation
Tins [65], 2000	Male, 69 years, thrombosed[a]	Amputation
Cho [66], 2005	Female, 66 years, symptomatic	Exclusion and PTFE graft
Bueno [67], 2005	Female, 32 years, ruptured	Resection (?), popliteo-tibioperoneal vein graft
Gutarra [42], 2007	Female, 38 years[b]	Resection and vein interposition graft

[a]Resulting from the medical history of the patient, who, at the age of 72, was studied for an aneurysm of the right coronary Valsalva sinus

[b]The patient had, along the same vascular axis, two femoral aneurysms (one ruptured) and one popliteal aneurysm, per se asymptomatic

The often acute presentation of aneurysms in NF-1 patients might suggest the opportunity of a screening for arterial lesions in all patients, through non-invasive methods, CT angiography, and MR angiography [8]. This would result something exaggerated and surely highly expensive due to the rarity of vascular involvement; however, agreement exists about a general screening in hypertensive patients, in patients with neurofibromas along the main peripheral vascular routes, and in those patients who have already presented a vascular complication of the disease (due to the frequent occurrence of multiple vascular lesions) [26, 42, 54]. Once diagnosed, asymptomatic vascular lesions and small aneurysms may be submitted to a close follow-up, as they may remain stable also after many years [4]. Surgical treatment may be difficult, in emergency cases, due to the fragility of the arteries and the propensity to profuse bleeding of the surrounding tissues; in the case of ruptured femoropopliteal aneurysm reported by Gutarra [42], very fine sutures (8/0 polypropylene) were used and a blood loss of 2000 ml was registered. Simple ligation or resection, when possible, is suggested to obviate prolonged operative times and dreadful complications [45]. The results of endovascular treatment look very attractive, mainly for the effective control of hemorrhage in ruptured aneurysms; stenting too may be really effective; however, there is the possibility of arterial wall damage during expansion of the stent edge [51].

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