Vascular abnormalities in patients with neurofibromatosis syndrome type I: Clinical spectrum, management, and results

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Purpose: **Neurofibromatosis type I (NF-I) is an autosomal dominant disorder affecting one in 3000 individuals. Vascular abnormalities are a well-recognized manifestation of NF-I. The purpose of this study is to review the spectrum, management, and clinical outcome of patients with vascular abnormalities and NF-I.**

Methods: **We retrospectively reviewed 31 patients (15 males, 16 females) with clinical NF-I and vascular abnormalities identified from imaging or operative findings between 1976 and 2005.**

Results: **The diagnosis of NF-I was made at a mean age of 11 ± 10 years with vascular lesions identified at a mean age of 38 ± 16 years. There were 76 vascular abnormalities, including 38 aneurysms, 20 arterial stenoses, 5 arteriovenous malformations (AVM), 5 arteries compressed or invaded by neural tumors, and 6 abnormalities of the heart valves. Arterial lesions were located in the aorta (n = 17) and in the renal (n = 12), mesenteric (n = 12), carotid-vertebral (n = 10), intracerebral (n = 4), and subclavian-axillary and iliofemoral arteries (3 each). Interventions were required in 23 patients (74%); 15 underwent 24 arterial reconstructions, including 9 renal, 8 aortic, 4 mesenteric, 2 carotid, and 1 femoral. The other eight patients had excision of AVM in three, vessel ligation in two, and clipping of cerebral aneurysms, coil embolization of hepatic aneurysms, and left thoracotomy in one patient each. One patient died of ruptured abdominal aortic aneurysm. Six patients (26%) had postoperative complications, including pneumonia in two, and stroke, acalculous cholecystitis, brachial plexopathy and chylothorax in one patient each. The median follow up was 4.1 years (range, 6 months to 20 years). Late vascular problems developed in three patients, including graft stenoses in two and rupture of another aortic aneurysm in one. Freedom from graft-related complications was 83% at 10 years. Patient survival at 10 years was 77%, less than the 86% expected survival for the general population ($P < .001$).**

Conclusion: **Patients with NF-I have a wide spectrum of vascular abnormalities, most notably aneurysms or stenoses of the aortic, renal, and mesenteric circulation. Operative treatment of symptomatic patients with vascular lesions or large aneurysms is safe, effective, and durable. (J Vasc Surg 2007;46:475-84.)**

Neurofibromatosis type I (NF-I), or von Recklinghausen disease, is an autosomal dominant disorder affecting one in 3000 individuals.[1] Cardinal features of NF-I include multiple café au lait macules, benign neurofibromas, and iris hamartomas.[1] Other common manifestations are learning disabilities, short stature, and skeletal abnormalities. Vascular lesions of medium and large-sized arteries and veins are a well-recognized, albeit rare, feature.[2,3] The term *NF-I vasculopathy* has been coined in the medical literature to describe aneurysms, stenoses, and arteriovenous malformations occurring in patients with NF-I.[3,4] The pathogenesis, clinical spectrum, and natural history of these abnormalities are unknown.

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Most patients with NF-I vascular abnormalities are asymptomatic but have involvement of multiple vessels.[2-4] Symptoms usually occur in childhood or early adulthood.[2-4] The renal artery is the most frequent site of involvement, and renovascular hypertension is the most common presentation.[2-4] Abdominal aortic coarctation, internal carotid artery aneurysms, and cervical vertebral arteriovenous malformations are other common manifestations.[2-4] The purpose of this study was to review the spectrum, management, and clinical outcome of patients with NF-I vascular abnormalities. In addition, a review of the English-language literature is summarized.

METHODS

We identified 31 patients with NF-I and vascular abnormalities from the vascular surgery and medical genetics registries who were evaluated at the Mayo Clinic in Rochester, Minnesota, between January 1, 1976, and January 1, 2005. Clinical diagnosis of NF-I was made from at least two of seven diagnostic criteria, as defined by the National Institutes of Health (NIH) consensus statement: six or more café au lait macules, two or more neurofibromas, axillary freckling, two or more Lisch nodules (iris hamartomas), sphenoid dysplasia or thinning of long bone cortex, or a first-degree relative diagnosed with NF-I.[1]

Vascular abnormalities included arterial or venous aneurysms, stenoses, arteriovenous malformations (AVM), and arterial compression or invasion by neural tumor. In general, criteria for operative or interventional treatment were presence of symptoms, rupture, or large aneurysm size. We used the same standard size recommendations (eg, abdominal aortic aneurysm, 5.5 cm) used for repair of aneurysms in patients without neurofibromatosis. Vascular lesions that were asymptomatic and aneurysms of small diameter were observed. Follow-up usually included annual physical examination and repeat imaging.

The pathologic specimens and radiologic studies were reviewed whenever possible. The medical records were reviewed for patient demographics, clinical characteristics, cardiovascular risk factors, operative data, and early and late morbidity and mortality. Late follow-up data were obtained from medical records, correspondence with referring physicians, telephone interviews, and from a detailed questionnaire sent to each patient. The National Death Index Search was used to document late mortality data, if needed. Survival curves were calculated using the Kaplan-Meier method and compared with the expected survival for age-matched and sex-matched controls from the State of Minnesota. Data was presented as median values or mean ± standard deviation, as appropriate. A value of $P < .05$ was significant. The study was approved by the Mayo Foundation Institutional Review Board.

RESULTS

Clinical characteristics. There were 15 male and 16 female patients with a mean age of 11 ± 10 years (range, <1 to 40 years) at time of NF-I diagnosis. The clinical diagnostic criteria and associated pathologic features are summarized in Table I. Café au lait macules and neurofibromas were most common, occurring in 94% of patients each, followed by inguinal or axillary freckling, or both, in 65%, and Lisch nodules in 42%. Positive family history was present in 15 patients (48%). Cardiovascular risk factors included hypertension in 16 patients (52%), cigarette smoking in 8 (26%), chronic renal insufficiency in 3 (10%), and hyperlipidemia, coronary artery disease, cerebrovascular disease, and chronic obstructive pulmonary disease in 2 patients each (6%).

Diagnostic investigation. Thirty patients (97%) underwent 75 radiologic studies. The abdominal vessels were imaged in 18 patients (60%), thoracic in 15 (50%), cervical in 14 (47%), and cerebral in 10 (33%). Contrast arteriography (Fig 1, *A* and *B*) was done in 23 patients (77%), 18 (60%) had computed tomography, 13 (42%) had magnetic resonance imaging, and 8 (26%) had ultrasound imaging. An echocardiogram was obtained in 11 patients (37%).

Vascular abnormalities. Seventy-six vascular abnormalities were identified in 31 patients (Table II). The first abnormality was diagnosed at an average age of 38 ± 16 years (range, 3 to 77 years). Forty lesions carried symptoms and 37 did not. Vascular abnormalities included 40 aneurysms in 18 patients, 20 arterial stenoses in 7, 5 AVM in 5 patients, and 5 arteries compressed or invaded by neural tumors in 4 patients. These lesions were found most often in the aortic (n = 17), renal (n = 12), mesenteric (n = 12), and carotid-vertebral circulations (n = 10). Five patients had six heart valve abnormalities, including mitral valve and aortic valve regurgitation in two patients each, and mitral valve prolapse and aortic valve stenosis in one patient each.

Table I. National Institutes of Health diagnostic criteria* in 31 patients with vascular abnormalities associated with neurofibromatosis syndrome type I

Clinical features	*Patients (n)*	*Percent*
NIH diagnostic criteria		
Café au lait macules	29	94
Neurofibromas	29	94
Inguinal or axillary freckling	20	65
First-degree relative with NF-I	15	48
Lisch nodules	13	42
Sphenoid bone dysplasia	2	6
Cortical long bone thinning	2	6
Associated pathology		
Scoliosis	5	16
Pseudoarthrosis	4	13
Malignant tumor degeneration	2	6
Optic nerve glioma	1	3
Pheochromocytoma	1	3
Gray matter ectopia	1	3
Mental retardation	1	3
Hydrocephalus	1	3

NIH, National Institutes of Health; *NF-1,* neurofibromatosis.
*National Institutes of Health (NIH) consensus conference statement, 1988.

Pathologic findings. Eight patients had 16 pathologic specimens reviewed. Five patients (age, 3 to 32 years) had four renal, two mesenteric, and two supraceliac aortic specimens reviewed. The histology in this group showed vascular dysplasia without evidence of atherosclerosis. Specific findings were fibromuscular dysplasia with neointimal thickening in all renal lesions (Fig 1, *C*), proliferation of Schwann cells and fibroblasts associated with plexiform neurofibroma and fibromuscular dysplasia of small vessels, and false aneurysm associated with neointimal thickening in the supraceliac aortic aneurysm. A 73-year-old patient with a giant thrombosed true internal jugular vein aneurysm had stretched disrupted elastic fibers and thick organizing granulation tissue consistent with low-grade inflammatory response on microscopy.

The two other patients, age 77 and 74 years, were treated for abdominal aortic aneurysms. One patient died from ruptured aneurysm and at autopsy was found to have five other asymptomatic aneurysms involving both internal carotid, both vertebral, and the basilar arteries. The seven arterial specimens from these two patients showed atherosclerotic changes without vascular dysplasia.

Operative treatment. A total of 41 vascular abnormalities (Table II and III) were repaired in 23 patients (74%). Indications included renovascular hypertension in 7 patients, large aneurysm size or rupture in 6, pain in 4, malignancy in 2, and chronic mesenteric ischemia, disabling claudication, sub-

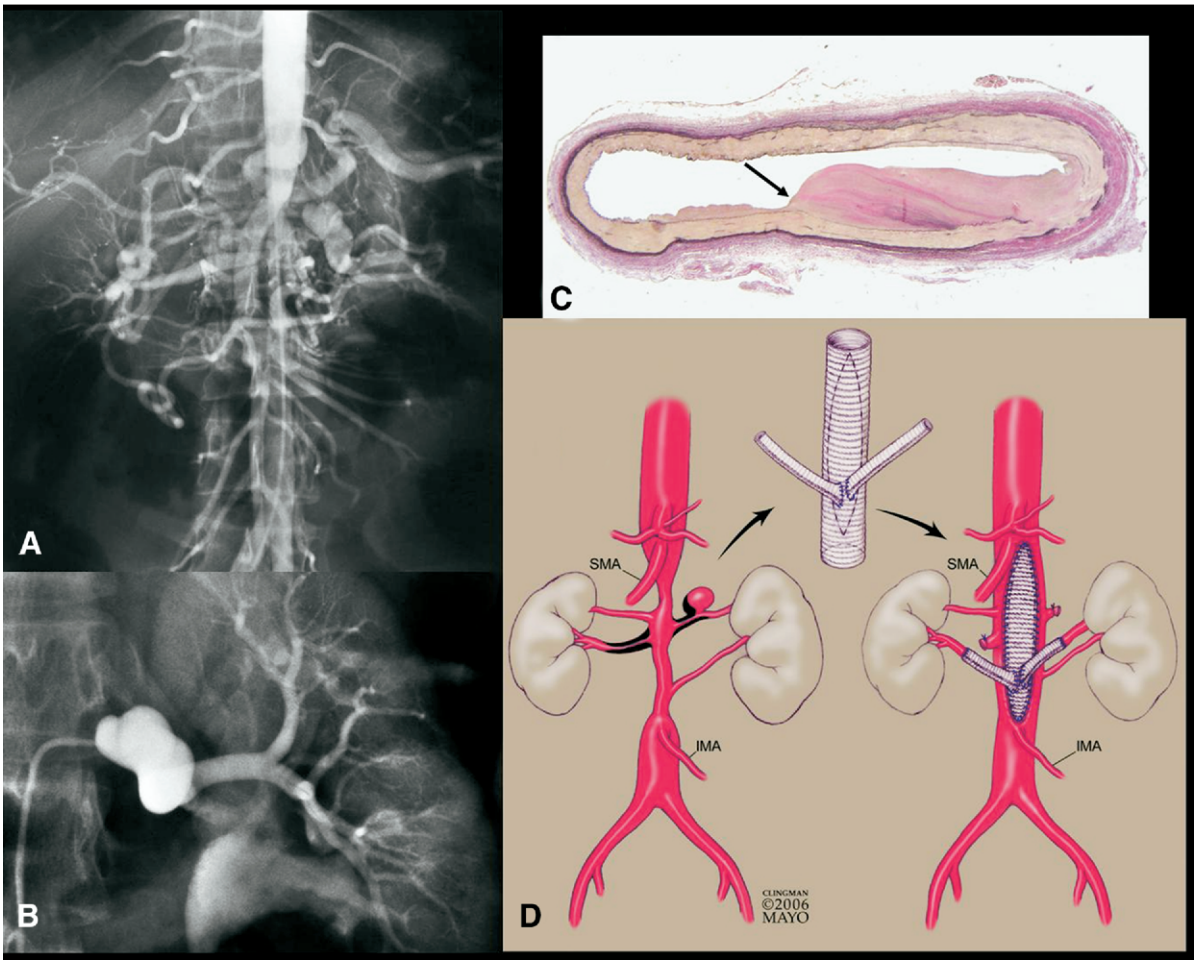

Fig 1. A, Abdominal aortogram and selective renal angiography reveals abdominal aortic coarctation **B**, with bilateral renal artery stenoses and a large left renal artery aneurysm. **C**, Renal artery specimen shows fibromuscular dysplasia with predominance of neointimal thickening *(arrow)*. **D,** The artist's illustration summarizes preoperative angiographic findings and the operative treatment with a longitudinal abdominal aortoplasty and bilateral renal artery bypasses. *SMA,* Superior mesenteric artery; *IMA,* inferior mesenteric artery.

arachnoid hemorrhage, and external bleeding from arteriovenous malformation in 1 patient each.

One or more arterial reconstructions were done in 15 patients. Six patients required 9 aortorenal artery bypasses, 4 with polyester, 3 with saphenous vein, and 2 with internal iliac artery. Eight patients had aortic reconstructions, which consisted of 4 aortoaortic grafts, 2 abdominal patch aortoplasties (Fig 1, *D*), 1 aortobiiliac, and 1 aortobifemoral graft. Three patients needed four mesenteric reconstructions, including three aorta-superior mesenteric artery bypasses and 1 celiac patch angioplasty. Femoral-femoral, carotid-carotid, and carotid-axillary artery bypass was done in 1 patient each. The interventions in the remaining eight patients included excision of a symptomatic AVM in three, and 1 patient each had primary ligation of a left subclavian artery, excision of a giant thrombosed internal jugular vein aneurysm, clipping of multiple cerebral aneurysms, coil embolization of multiple hepatic aneurysms, and resuscitative left thoracotomy.

One intraoperative death from ruptured abdominal aortic aneurysm occurred among the 23 patients who required interventions. Intraoperative bleeding requiring transfusion occurred in two patients because of increased vascular fragility. One patient had a giant internal jugular vein aneurysm and the other had a 5-cm left subclavian artery aneurysm. In both cases, multiple pledgeted sutures were required to obtain hemostasis. Six patients (26%) presented with postoperative complications, including pulmonary problems in two, and a large middle cerebral territory stroke, acute acalculous cholecystitis, brachial plexopathy, and chylothorax in one each. The median length of stay was 8 days (range, 3 to 105 days).

Conservative treatment. Seventeen asymptomatic patients with 35 vascular abnormalities were treated conser-

Table II. Distribution of 76 vascular abnormalities in 31 patients with neurofibromatosis type I

	Vascular abnormalities		*Treatment*			
			Operative		*Conservative*	
Location	*Lesions (n)*	*Patients (n)*	*Lesions (n)*	*Patients (n)*	*Lesions (n)*	*Patients (n)*
Aneurysms	40	18	19	12	21	15
Internal carotid artery	6	4	1	1	5	3
Cerebral	4	3	1	1	3	2
Ascending aorta	4	4	0	0	4	4
Abdominal aorta	5	5	5	5	0	0
Renal artery	3	3	2	2	1	1
Vertebral artery	3	2	0	0	3	2
Descending thoracic aorta*	2	2	2	2	0	0
Hepatic artery	2	1	2	1	0	0
Internal jugular vein	2	1	1	1	1	1
TAA aorta	1	1	0	0	1	1
Common iliac artery	3	2	2	1	1	1
Subclavian artery	1	1	1	1	0	0
Axillary artery	1	1	0	0	1	1
Gastroduodenal artery	1	1	1	1	0	0
Pancreaticoduodenal artery	1	1	1	1	0	0
Lumbar artery	1	1	0	0	1	1
Stenoses	20	7	15	7	5	2
Renal artery	9	6	9	6	0	0
Abdominal aortic coarctation	4	4	3	3	1	1
Celiac artery	3	3	1	1	2	2
Superior mesenteric artery	3	3	1	1	2	2
TAA coarctation	1	1	1	1	0	0
Arteriovenous malformations	5	5	3	3	2	2
Extremity	2	2	1	1	1	1
Thoracic vertebral	1	1	0	0	1	1
Cervical vertebral	1	1	1	1	0	0
Facial	1	1	1	1	0	0
Arterial compression	3	2	3	2	0	0
Subclavian	1	1	1	1	0	0
Celiac axis	1	1	1	1	0	0
Superior mesenteric artery	1	1	1	1	0	0
Tumor invasion	2	2	2	2	0	0
Superficial femoral artery	1	1	1	1	0	0
Common carotid artery	1	1	1	1	0	0
Heart valves	6	5	0	5	6	5
Total†	76	31	41	23	35	17

TAA, Thoracoabdominal aortic.
*One patient had a descending thoracic aneurysm repaired elsewhere.
†Several patients had multiple vascular lesions.

vatively. There were 21 aneurysms that were considered too small for repair. Another two aneurysms in the cavernous and supra-clinoid portion of the internal carotid artery were observed because of difficult access for repair. Follow-up included annual physical examination and radiologic imaging at 6-month to 18-month intervals, depending on the size and location of the aneurysms.

Late outcome. The 30 survivors were followed up for a median of 4.1 years (range, 6 months to 19.7 years). Repeat imaging studies were done in 21 patients (70%). Twenty-seven patients were asymptomatic and did not develop any late vascular problem. All patients with renovascular hypertension were either cured or had improved blood pressure control on smaller doses of antihypertensive medications. One patient who was treated conservatively for an ascending aortic aneurysm died of ruptured aneurysm 2.6 years later.

Survival free of secondary vascular or graft-related complications in 21 patients with repeat imaging study was 90% at 1 year (Greenwood standard deviation [GSD], 6.6%) and 83% at 10 years (GSD, 9.4%). Overall, secondary complications developed in three (20%) of 15 patients who had arterial reconstructions. A 72-year-old woman with multiple comorbidities died of a ruptured ascending aortic aneurysm 2.6-years after repair of a descending thoracic aneurysm. A 32-year-old man treated for chronic mesenteric ischemia with a bypass from the aorta to the superior mesenteric artery developed graft thrombosis 20-months after operation. A bypass from the aorta to the common hepatic artery was performed, and he is asymptomatic 19 years later. A 33-year-old woman who had bilateral aorta-to-renal saphenous vein grafts presented with recurrent renal artery stenosis at both sites 16 months postoperatively. She

underwent a redo left renal artery bypass with prosthetic and a bovine patch angioplasty of the right distal anastomosis. The right aorta-to-renal graft occluded 6 months after the revision and she needed a right nephrectomy. The aorta-to-left renal artery bypass is patent 14 years after the operation, and her hypertension remains well controlled.

Overall patient survival at 10 years was 77% (GSD, 6.8%), less than the 87% expected for an age-matched and sex-matched population of the State of Minnesota ($P < .001$, Fig 2). Six patients (20%) died during follow-up, four from malignancy, one from ruptured ascending aortic aneurysm, and one from an unknown cause. Two of the malignancies were neurofibrosarcoma.

DISCUSSION

Neurofibromatosis type I is an autosomal dominant disorder resulting from a mutation of the NF-I gene located on the long arm of chromosome 17 (17q11.2).[2-4] Although the NF-I gene mutation has nearly complete penetrance and will cause some clinical manifestations by adulthood, its expressions are highly variable. The protein product of the gene, *neurofibromin,* shares sequence and functional homology with the *ras* oncogene, a tumor suppressor gene. Therefore, loss of neurofibromin produces increased mitogenic signaling and leads to increased cellular proliferation or differentiation. For this reason, the NF-I gene mutation is associated with multiple neoplasms, most commonly malignant nerve sheath tumors, myelogenous leukemia, pheochromocytoma, and neurofibromas.[2-5]

Intrinsic lesions of the arterial wall are important manifestations of NF-I, yet the pathogenesis of these lesions remains ill defined. Reubi[6] first classified the vascular histology into intimal, aneurysmal or fusocellular forms. A common finding between the types is spindle cell proliferation. Other authors believe that the vascular lesions develop either by proliferation of nerves within the vessel walls or from compression or invasion by neural tumors.[3] This latter theory does not correlate well with clinical findings, however. More often, the histologic feature is fibromuscular dysplasia with a predominance of intimal thickening.[4]

It may be that arterial stenoses or aneurysms in these patients occur by a dynamic process of cellular proliferation, degeneration, healing, smooth muscle loss, and fibrosis. Moreover, neurofibromin expression has been demonstrated in the vascular endothelial and smooth muscle cells. This suggests that deficiency in neurofibromin in NF-I may cause proliferation within the vessel wall, a process analogous to that which produces multiple cutaneous neurofibromas.[3]

The term *NF-I vasculopathy* has been used by medical geneticists to describe the vascular lesions in NF-I.[3-4] The frequency of this vasculopathy is hard to define because screening studies are not routinely done, but the prevalence of vascular lesions in large clinical series is 0.4% to 6.4%.[2-4] Lin et al[2] found a 2% prevalence of cardiovascular abnormalities among 2322 participants in the National Neurofibromatosis Foundation database. Only 16 patients (0.7%) had peripheral artery abnormalities, including nine (0.4%) with renal artery stenoses. These numbers likely underestimate the true prevalence of these lesions because radiologic studies are reserved for symptomatic patients or in those suspected of having a vascular abnormality.

We found vascular lesions in NF-I patients aged ≤50 years to differ in type, location, and histology compared with older patients. We identified a predominance of aortic, renal, mesenteric, and carotid-vertebral stenoses or aneurysms in the younger patients, whereas the older ones had degenerative atherosclerotic aortic aneurysms. Although atherosclerosis typically involves the origin or bifurcation of large arteries, NF-I vascular lesions often do not. For example, the renal and mesenteric arterial lesions in our patients were often long and tapered and extended into the primary branches of the artery but spared its aortic origin. Aortic aneurysms involved the ascending or thoracoabdominal aorta more often than the infrarenal segment. Furthermore, the histologic specimens from younger patients showed fibromuscular dysplasia or spindle cell proliferation in striking contrast to the degenerative atherosclerotic changes in older patients. The reasons why lesions develop in some patients at a young age and in others at an older age, and how NF-I impacts the development of atherosclerosis, are unclear.

A review of the English-language literature from 1957 to 2005 yielded 237 patients with NF-I who had 320 vascular abnormalities, including the 31 patients reported here.[2,7-40] Renal artery lesions are most common (41%), are unilateral in 68%, and are more often stenotic than aneurysmal. Renal artery disease was diagnosed between the ages of 11 and 21 years (Table IV). Renal artery aneurysms are often intrarenal, which precludes arterial reconstruction in some patients. The carotid, vertebral, or cerebral artery lesions seen in 19% of patients are commonly aneurysms, occur in the third decade of life, and occur more often in women (72%). Abdominal aortic coarctation or aneurysms, with or without renal and mesenteric involvement, have been reported in 12%.

Treatment depends on the patient's age and the type and location of the lesion. Isolated renal artery disease has been treated with open or endovascular techniques, nephrectomy, or medical therapy (Table V, online only).[7-23] Open renal artery reconstruction has been done in 45 of the 97 reported cases, the plurality done with an autologous aortorenal artery bypass. Hypertension was cured or improved in 38 patients (84%), but recurrent stenosis developed in seven (15%). Percutaneous transluminal angioplasty was used to treat 21 lesions in 18 patients, but eight (44%) presented with restenosis requiring another intervention. Medical therapy alone was used in 18 patients, but six failed therapy. Nephrectomy was the sole treatment in 16 patients. Given these data, our preference is to perform open reconstruction with an aortorenal artery autologous bypass.

The aorta may be aneurysmal or stenotic. Aneurysms predominate in patients aged >50, whereas abdominal aortic coarctation occurs more often in younger patients.[13,20-24] In our opinion, the indications for treatment

Table III. Clinical presentation, treatment, and results in 31 patients with vascular abnormalities and neurofibromatosis type I

Patient	*Age, sex*	*No. NIH criteria*	*Cardiovascular abnormalities*	*Clinical presentation*	*Treatment*	*Early outcome*	*Late outcome**
Conservative treatment							
1	18M	2	R forearm AVM		Conservative		Asymptomatic, 15 yr FU
2	72M	5	R common iliac artery aneurysm, MVR	Asymptomatic	Conservative		Asymptomatic, 4.5 yr FU
3	20F	4	Ascending aortic aneurysm, AVR	Asymptomatic	Conservative		Asymptomatic, 4.3 yr FU
4	50F	5	Bilateral internal carotid artery aneurysms	Asymptomatic	Conservative		Asymptomatic, 14 yr FU
5	75M	2	Ascending aortic and TAAs, MVR and AVR	Asymptomatic	Conservative		Died: cholangiocarcinoma, 18 mon FU
6	20F	3	R internal carotid artery aneurysm	Asymptomatic	Conservative		Asymptomatic, 11 mon FU
7	21M	4	R RAA	Asymptomatic	Conservative		Died: NF-I– related cancer, 12 yr FU
8	7M	4	Thoracolumbar spine AVM	Asymptomatic	Conservative		Asymptomatic,16 yr FU
Operative treatment							
9	6F	3	Abdominal aortic coarctation, bilateral RA stenoses	Renovascular hypertension	Abdominal aortoplasty, bilateral RA bypass	No comp	Improved BP control, 3 yr FU
10	9M	2	Abdominal aortic coarctation, right RA and SMA stenoses	Renovascular hypertension	Supra-celiac to infra-RA bypass, aorto-RA and aorta-SMA bypass	No comp	Cured BP, 8 mon FU
11	17M	3	Abdominal aortic coarctation, bilateral RA stenoses, and L RAA	Renovascular hypertension	Abdominal aortoplasty, bilateral RA bypass	No comp	BP cured at 11.5 years FU
12	3F	4	R RA, celiac and SMA stenoses	Renovascular hypertension	Aorto-RA bypass	No comp	BP improved, 14 yr FU
13	33F	2	Bilateral RA stenoses	Renovascular hypertension	Bilateral aorto-RA bypass	No comp	Recurrent L RA stenosis, R RA occlusion at 16 mon FU; redo L RA bypass, R nephrectomy. BP improved, 14 yr FU
14	26M	3	Mild aortic stenosis, celiac, and SMA stenoses, L RA occlusion with large RAA, and multiple lumbar artery aneurysms	Renovascular hypertension	Resection of RAA and aorto-RA bypass	No comp	BP cured, 5.6 yr FU
15	22F	4	TAA coarctation, supraceliac aortic saccular aneurysm, occluded celiac axis	Renovascular hypertension	Descending thoracic to pararenal aortic bypass, aorto-SMA bypass	No comp	BP cured, 4 years FU
16	77M	2	AAA	Large size	Aortoaortic graft	No comp	Asymptomatic, 5 yr FU
17	73F	3	R internal jugular vein aneurysm, L internal jugular vein ectasia	Large size	R internal jugular vein ligation	Vascular fragility, intra-op pulmonary embolism	Asymptomatic, 22 mon FU
18	43F	3	Prior ruptured TAA, 5-cm L subclavian aneurysm, and vertebral and middle cerebral artery aneurysms	Large size	L subclavian artery ligation, carotid-subclavian artery bypass	Brachial plexopathy, vascular fragility, bleeding	Asymptomatic, 7.5 yr FU

Table III. Continued.

Patient	*Age, sex*	*No. NIH criteria*	*Cardiovascular abnormalities*	*Clinical presentation*	*Treatment*	*Early outcome*	*Late outcome**
19	72F	5	Ascending aortic and descending TAA, AVS	Large size	Aortoaortic graft	No comp	Died: ruptured ascending AA, 2.6 yr FU
20	68M	5	Ascending aortic, axillary, AAA, and bilateral common iliac artery aneurysms	Large size	Aortobiiliac bypass	Pneumonia	Died: unknown cause, 4 mon FU
21	74M	2	Ruptured AAA; bilateral internal carotid and vertebral and basilar artery aneurysms	Pain	Left thoracotomy for resuscitation	Intra-op death	
22	16F	4	Large facial AVM	Bleeding	Total excision	No comp	Asymptomatic, 4.3 yr FU
23	32M	3	Celiac and superior mesenteric artery occlusion	Chronic mesenteric ischemia	Aorto-SMA bypass, celiac axis patch angioplasty	No comp	Occluded graft, 20 mon FU; redo aortohepatic artery bypass; asymptomatic, 19 yr FU
24	71M	4	AAA with aortoiliac occlusive disease, MVP	Disabling claudication	Aortobifemoral bypass	No comp	Asymptomatic,6 yr FU
25	21M	3	L subclavian artery stenosis	Pain	L subclavian artery ligation, resection of neurofibroma	Chylothorax treated conservatively	Asymptomatic at 20 mon FU
26	12F	3	Multiple (4) gastroduodenal and hepatic artery aneurysms	Pain	Coil embolization	Acute acalculous cholecystitis, cholecystectomy	Asymptomatic, 10.6 yr FU
27	41F	5	L lower extremity AVM	Pain	Partial excision	No comp	Asymptomatic, 6 mon FU
28	28F	3	Cervical vertebral artery AVM	Pain	R vertebral artery ligation, resection of AVM	No comp	Asymptomatic, 5 yrs FU
29	32F	5	R femoral artery stenoses due to tumor invasion	Malignancy	Wide local excision, femoral artery interposition graft	No comp	Died: tumor recurrence, 3.5 yr FU
30	44M	2	Tumor invasion of R common carotid artery	Malignancy	Wide local excision, carotid artery interposition graft	No comp	Died: tumor recurrence, 6 mon FU
31	43F	2	R internal carotid, middle cerebral and temporal artery aneurysms	Subarachnoid hemorrhage	Clipping of R internal carotid and middle cerebral artery aneurysms	R hemispheric stroke	Permanent deficit, 2 yr FU

NIH, National Institutes of Health; *AAA*, abdominal aortic aneurysm; *AVM*, arteriovenous malformation; *FU*, follow-up; *RA*, renal artery; *RAA*, renal artery aneurysm *MVR*, mitral valve regurgitation; *TAA*, thoracoabdominal aortic aneurysm, *AVR*, aortic valve regurgitation; *MVP*, mitral valve prolapse; *AVS*, aortic valve stenosis; *SMA*, superior mesenteric artery; *BP*, blood pressure; *No comp*, no complications; *NF-1*, neurofibromatosis type I.
*Patients were alive at follow-up, unless indicated otherwise.

in either circumstance should be the same as for patients without NF-I. In general, we offer repair of abdominal aortic aneurysms ≥5.5 cm in diameter, and thoracoabdominal aneurysms ≥6.0 cm, depending on the patient's age and comorbidities.

Although there are no reports of endovascular repair for aneurysms associated with NF-I, this approach could be applied to select older patients. We noted no fragility of the aorta or abdominal branch arteries during open repair, but two patients with aneurysms, one jugular vein and the other subclavian artery, had friable vessels. Therefore, some precautionary measures are appropriate. We recommend gentle, atraumatic, and delicate handling of tissues, careful placement of retractors, and use of soft, protected arterial clamps. We are unaware of any reports showing increased risk of complications with diagnostic angiography and other catheter-based procedures in NF-I patients.

Table IV. Summary of case reports and literature reviews of reported cases of vascular abnormalities in patients with neurofibromatosis type I

Type and location of vascular lesion	*Reference*	*Patients (n)*	*Lesions (n)*	*Mean age (yr)*	*Range*	*Male/Female*
Isolated renal artery disease	7-22	97	129	12.5	0.4-46	46M/51 F
Unilateral		65	65	12.5	2-34	31M/34 F
Bilateral		32	64	10.5	0.4-46	15M/17 F
Stenosis		86	117	11.2	0.4-34	42M/44 F
Aneurysm		11	12	21.4	6-46	4M/7 F
Isolated mesenteric artery disease	23	5	11	36.5	12-55	1M/4 F
Stenosis		1	2	32	12	M
Aneurysm		4	9	37.2	14-55	0M/4 F
Abdominal/distal thoracic coarctation	13, 20-24	17	52	11.2	1.3-26	9M/8 F
Associated renal disease		16	25	11.8	1.3-26	9M/7 F
Associated mesenteric disease		6	8	15.1	11-26	3M/3 F
Aortic aneurysm or dissection	25-27	13	14	59.5	20-77	6M/3 F
Ascending aorta		4	4	43	20-74	2M/2 F
Descending aorta		4	4	64	45-75	2M/2 F
Thoracoabdominal aorta		1	1	75	30	M
Abdominal aorta		4	4	73	68-77	4M/0 F
Carotid, vertebral and cerebral aneurysms	28-32	46	54	34.7	1-60	13M/33 F
Internal carotid artery aneurysm		22	26	29.3	1-60	5M/17 F
Vertebral artery aneurysm		12	13	44.8	0.5-59	2M/10 F
Cerebral artery aneurysm		12	15	30.1	7-60	6M/6 F
Subclavian or innominate artery disease	33-35	15	15	38.1	9-61	4M/11 F
Aneurysm/dissection/rupture		13	13	45.8	32-61	3M/10 F
Stenoses		2	2	15	9-21	1M/1 F
Axillary, brachial, radial artery aneurysm	36	4	4	40.6	30-74	3M/1 F
Arteriovenous malformations	37-38	32	32	35.8	11-60	6M/26 F
Cervical vertebral		22	22	38.1	11-60	3M/19 F
Lumbar spinal		2	2	8.5	7 and 10	1M/1 F
Trunk/extremity		5	5	39.3	18-59	1M/4 F
Facial		3	3	34	16-58	1M/2 F
Other miscellaneous lesions	39-40	8	9	52.1	11-73	1M/7 F
Infrainguinal artery aneurysm		6	6	39.1	11-72	1M/5 F
Internal jugular vein aneurysm		2	3	67.5	62 and 73	0M/2 F
Total		237	320	25.6	0.4-77	85M/134 F

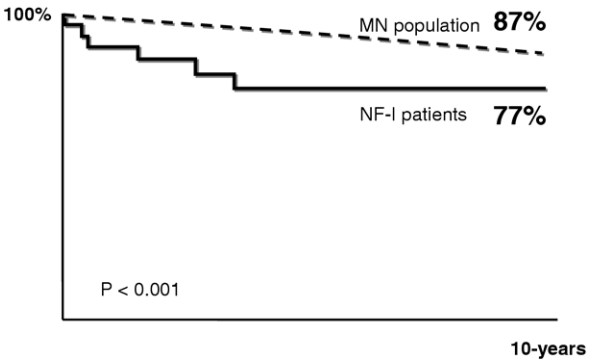

Fig 2. Kaplan-Meier estimates of overall survival for patients with neurofibromatosis-1 *(NF-I, solid line)* are compared with age-matched and sex-matched controls of the general population of the State of Minnesota *(MN, dashed line)*.

Open reconstruction is offered to patients with abdominal aortic coarctation who have renovascular hypertension unresponsive to medical therapy, chronic mesenteric ischemia, disabling claudication, or combinations thereof. The aorta is frequently narrowed in the paravisceral segment, although we, and others, have reported distal thoracic involvement.[20-24] Supraceliac-to-infrarenal aortic bypass or patch aortoplasty are the treatment options. We favor a midline, transperitoneal approach with medial visceral rotation in most patients, or a low left thoracoabdominal approach if the distal thoracic aorta is involved. A supraceliac-to-infrarenal aorta bypass with end-to-side anastomoses is preferred for patients with a long (>5 to 6 cm) narrowed aortic segment. This technique minimizes renal and mesenteric ischemia time and allows placement of a larger graft in children whose aorta will still grow. Additional grafts to the renal and mesenteric arteries are done as needed. Abdominal aortoplasty is reserved for patients with a focal narrowing of the aorta but may be used in conjunction with aortic bypass in cases of long segment stenosis.

Other manifestations of NF-I vasculopathy deserve comment. From the literature review, carotid, vertebral, and cerebral aneurysms, reported in 46 patients, occur in the third decade of life and are more frequent in women (72%). Cervical vertebral AVM are a classic presentation and may be the late result of contained ruptured vertebral artery aneurysms. Spontaneous subclavian artery rupture, upper and lower extremity aneurysms, and AVM of the

face, trunk, and extremities have been documented.[25-40] Our patient with the giant internal jugular vein aneurysm is the second one to be reported in the literature.[40]

Survival is shorter in patients with NF-I compared with the general population.[5] An analysis of United States death certificates shows that patients with NF-I die at a median age of 59 years, 15 years younger than controls matched for age and sex.[5] The most common cause of death is malignancy, often from connective and soft-tissue neoplasms. Vascular disease is the second leading cause of death, especially among those individuals aged <40 years old.[5] Our outcome data are similar.

The role of routine vascular screening has not been evaluated. Because clinically significant lesions are relatively uncommon (2%), periodic vascular assessment cannot be recommended to all NF-I patients. Instead, we currently advocate selective imaging if there is clinical suspicion. If a vascular abnormality is identified on initial screening study (eg, renal ultrasound imaging for hypertension), noninvasive imaging (computed tomography angiography or magnetic resonance angiography) of the head, chest, and abdomen is justifiable because of the multiplicity of lesions in some patients. In our opinion, recommendations for follow-up study should be the same as for patients without NF-I.

CONCLUSION

Patients with NF-I have a wide spectrum of vascular lesions. Aneurysms or stenoses of the aortic, renal, and mesenteric arteries are the most common lesions. Most lesions occur by age 50 years and are due to an underlying vasculopathy. Operative treatment of patients with symptomatic disease or large aneurysms is safe, effective, and durable.

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AUTHOR CONTRIBUTIONS

Conception and design: GO, TS
Analysis and interpretation: GO, TS, TB, PG
Data collection: GO, DM, DB, TM, AS
Writing the article: GO, TS, TB
Critical revision of the article: GO, TS, TB, PG, DM, DB, TM, AS
Final approval of the article: GO, TS, TB, PG, DM, DB, TM, AS
Statistical analysis: GO
Obtained funding: GO, TS, TB, PG, AS
Overall responsibility: GO

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Table V (online only). Results of treatment of isolated renal artery lesions and abdominal aortic coarctation with concomitant renal and/or mesenteric artery disease in patients with neurofibromatosis type I

Type of lesion	*Reference*	*Patients (n)*	*Lesions (n)*	*Mean FU*	*Cured/Improved*	*Worse/Recurred*
Renal artery disease	7-22					
Open arterial reconstruction		45	67	47 ± 65	38	7
Autologous		27	38	44 ± 58	25	2
Prosthetic		7	11	28 ± 27	4	3
Not specified		11	18	87 ± 80	9	2
Percutaneous angioplasty		18	21	27 ± 29	10	8
Nephrectomy		16	16	25 ± 58	13	3
Medical therapy		18	25	11 ± 20	12	6
Abdominal aortic coarctation	13, 20-24					
Aortoplasty/bypass		17	52	56 ± 62	13	4

FU, Follow-up.