European Journal of Radiology 100 (2018) 66–75

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

The endovascular management of neurofibromatosis-associated aneurysms: A systematic review☆

David Bargiela[a,b], Misha M. Verkerk[a,c], Ian Wee[a,d], Kiera Welman[a,e], Eugene Ng[a,f], Andrew M.T.L. Choong[a,g,h,*]

[a] SingVaSC, Singapore Vascular Surgical Collaborative, Singapore
[b] Department of Physiology, Development and Neuroscience, University of Cambridge, UK
[c] Ear, Nose and Throat Department, St George's Hospital, London, UK
[d] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[e] Hervey Bay Hospital, Pialba, Queensland, Australia
[f] Department of Vascular Surgery, Westmead Hospital, Westmead, New South Wales, Australia
[g] Division of Vascular Surgery, National University Heart Centre, Singapore
[h] Department of Surgery, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

ARTICLE INFO

Keywords:
Neurofibroblastoma
Von Recklinghausen
Aneurysm
Vasculopathy
Endovascular surgery

ABSTRACT

Background: Neurofibroblastoma (NF) or Von Recklinghausen disease, is an autosomal dominant disorder affecting one in 3000 individuals. Cardinal features of NF include multiple café-au-lait macules, benign neurofibromas, and iris hamartomas. Albeit less common, vascular lesions of medium and large-sized arteries and veins are a well-recognized complication, which can lead to fatal consequences such as rupture.

Method: A systematic review was conducted as per the Preferred Reporting Instructions for Systematic Reviews and Meta-analysis (PRISMA) guidelines utilizing PubMed, EMBASE, and Cochrane databases.

Results: There were 59 articles identified involving 66 patients (mean age 44.3 ± 30 years), of which 89% had neurofibromatosis type 1. There were 63.6% of patients who presented with aneurysm rupture, 33.3% presented with intact symptomatic aneurysms, and 3.1% presented with intact asymptomatic aneurysms. Anatomically, 4.5% of patients suffered from intracranial aneurysms; 12.1% suffered from visceral artery aneurysms (including hepatic, superior mesenteric, gastroduodenal and renal arteries), and other patients suffered from aneurysms within the chest, abdomen, pelvis, upper limbs and neck. Amongst the various endovascular procedures, coiling was performed in 83.3% of cases. There were 12 covered stents employed in 10 patients (18.2%), of which 7 were balloon-expandable grafts; 2 were self-expandable graft; 3 were not mentioned. The rates of major and minor complications were 15% and 6% respectively, with 4 cases (6%) of perioperative death. On a mean follow-up of 15 months (range 1.5–72 months), two patients developed a distant vascular lesion from the treated lesion.

Conclusion: Endovascular management is safe and effective even in hemodynamically unstable neurofibroblastoma patients at all ages. Vascular tree screening should be conducted in clinically suspicious patients to prevent fatal aneurysmal complications. A formal meta-analysis could not be performed due to the lack of randomized controlled trials.

1. Introduction

Neurofibromatosis is an autosomal dominant disorder linked to chromosome 17, with an estimated prevalence of 1 per 3000–4000 subjects [1]. Type 1 neurofibromatosis (also known as von Recklinghausen disease) is the most common subtype, characterised by the formation of benign neurofibromas, cutaneous café-au-lait spots and iris hamartomas [2]. Other notable features include aneurysmal and occlusive vascular lesions, learning disability and skeletal abnormalities. Type 2 neurofibromatosis is characterised by bilateral vestibular schwannomas and is less commonly associated with vascular anomalies [3–5].

The spectrum of vasculopathy in neurofibromatosis includes aneurysms, stenosis and arteriovenous malformations of medium and

☆ The authors do not have any sources of financial support, and any conflicts of interest. This paper has been presented at the 20th Annual Meeting of The Asian Society for Cardiovascular and Thoracic Surgery (8th–11th March 2012), and the Australian and New Zealand Society of Vascular Surgery Scientific Meeting (12th–15th October 2013).

* Corresponding author at: National University Heart Centre, Singapore, 1E Kent Ridge Road, Level 9, NUHS (National University Heath System) Tower Block, 119228, Singapore.
E-mail address: suramctl@nus.edu.sg (A.M.T.L. Choong).

https://doi.org/10.1016/j.ejrad.2017.12.014
Received 14 October 2017; Received in revised form 13 December 2017; Accepted 19 December 2017

Table 1
Patient characteristics and aneurysmal features.

No.	First author, year	Study design	Age	Gender (M/F)	NF types	Anatomical location	Size (mm)	Ruptured (Y/N)	Presentation
Intracranial aneurysms (n = 3)									
1	Lesley, 2004	CR	36	M	2	R MMA	4	N	R arm weakness; multiple meningiomas
2	Ellis, 2011	CR	9	F	1	R MCA	5	Y	Sudden LOC while tobogganing; R fixed and dilated pupil; R frontal ICH
3	Kanematsu, 2011	CR	48	M	1	2 × L occipital artery	–	Y	L neck pain and dyspoea; neck swelling
Neck artery aneurysms (n = 14)									
4	Teitelbaum, 1998	CR	34	F	1	Superficial cervical branch of left TCA	15	Y	Pain in upper back, shoulder and chest; dypsnoea; L hemothorax
5	Smith, 2000	CR	28	F	–	L ICA	–	Y	L neck swelling; headache
6	Arai, 2007	CR	38	M	–	L ascending CA and dissection of VA	–	Y	Chest pain, dizziness, vomiting, massive hemothorax
7	Sun, 2007	CR	57	F	–	L transverse CA	18	N	L neck pain and swelling
8	Ku, 2008	CR	28	F	1	2 × ICA	40	N	Bilateral neck swelling, cervical neuralgia, dysarthria, dysphagia
9	Chovanec, 2009	CR	37	M	1	L TCA	–	Y	L shoulder pain, LOC, L sided hemothorax
10	Kanematsu, 2011	CR	39	F	1	R ECA	–	Y	R neck swelling and pain
11	Moratti, 2012	CR	48	F	1	R cervical ICA	–	N	R pulsatile neck mass, cough, hoarseness, dysphagia
12	Hung, 2012	CR	47	F	1	L TCA	–	Y	L neck swelling and pain
13	Anpalakhan, 2013	CR	39	M	1	R TCA	20	N	R arm sensorimotor symptoms, neck vein distension
14	Hamasaki, 2014	CR	66	F	1	R ICA	–	N	Nil
15	Hoonjan, 2014	CR	43	M	1	Branch of L costocervical trunk	–	Y	L chest pain, L neck swelling
16	Lee, 2015	CR	18	M	1	L ICA	–	Y	Headache, tinnitus, nausea, vomiting
17	Leclerc, 2017	CR	73	M	1	L ICA	35	N	Two TIA in left middle cerebral artery region
Vertebral artery aneurysms (n = 16)									
18	Negoro, 1990	CR	42	M	1	L VA	–	Y	L suboccipital pain and swelling
19	Muhonen, 1991	CR	52	F	–	L VA at C2, 9 mm saccular aneurysm L ICA; 3 mm saccular from branch of L PCA	–	N	Mass (4 × 5 cm) on L side of neck with bruit; decreased hearing in L ear; weakness of L deltoid, trapezius and SCM muscles; hyperactive reflexes and ankle clonus in L lower extremity; L sided dysmetria
20	Ushikoshi, 1999	CR	40	F	1	L VA	–	Y	Occipital headache, large subcutaneous mass in suboccipital area
21	Horsley, 1997	CR	56	F	1	2 x L VA (C5-C6; C6-C7)	–	Y	Neck pain, R lateral forearm and thumb pain, decreased biceps jerk, L anterior triangle mass
22	Roth, 2000	CR	36	F	1	L VA	–	Y	L shoulder/neck/arm pain and weakness; L leg weakness; respiratory failure owing to tracheal deviation; L neck/chest wall mass
23	Hidea, 2007	CR	36	F	1	L VA (ostium)	49	Y	Hemoptysis; back pain; chest pain; dyspnoea; hypotension; coma
24	Hiramatsu, 2007	CR	67	M	1	L VA	20	N	Persistent dizziness, bruit in L supraclavicular region
25	Peyre, 2007	CR	18	F	1	R VA at C6	25	N	C6 radiculopathy
26	Horie, 2008	CR	30	F	1	R VA at C6-C7	–	N	C6 radiculopathy
27	Sandhu, 2008	CR	42	F	–	L VA	–	Y	Chest pain and dyspnoea; large neurofibroma on L lower neck and upper chest;pleural effusion, haemothorax
28	Higa, 2010	CR	60	F	1	L VA	–	Y	Neck hematoma; stridor; respiratory failure
29	Hiramatsu, 2012	CR	31	M	1	R VA	–	N	R neck and shoulder pain, neck hematoma
30	Anpalakhan, 2013	CR	39	M	1	R TCA	20	N	R arm sensorimotor symptoms, neck vein distention and weight loss
31	Hamasaki, 2014	CR	66	F	1	R ICA	–	N	Nil
32	Uneda, 2016	CR	35	F	1	R cervical VA	–	N	R neck and shoulder pain
33	Strambo, 2017	CR	53	M	1	L VA	40	N	Acute onset of nausea, vomiting, and gait unsteadiness, dysarthria, right sided paresthesia, left limbs ataxia, right lateral homonymous hemianopia secondary to ischemic stroke
Subclavian artery (n = 3)									
34	Kim, 2005	CR	45	F	1	L SCA	36	Y	L shoulder pain and swelling, dysponea, hemothorax
35	Sakamoto, 2009	CR	51	M	1	L SCA	8	Y	L neck pain, dysphagia
36	Mydin, 2015	CR	56	F	1	R SCA	–	Y	R chest pain, collapse, dyspnoea, R hemothorax
Intercostal artery aneurysms (n = 13)									
37	Kipfer, 2001	CR	42	F	1	R intercostal artery	–	Y	Chest pain, LOC, hemothorax
38	Dominguez, 2002	CR	44	M	1	L 4th intercostal	10	Y	Pleuritic pain; dyspnoea; haematic pleural effusion
39	Chang, 2005	CR	29	M	1	R 7th intercostal	–	Y	Dyspnoea, retrosternal pain radiating to back

(*continued on next page*)

Table 1 (*continued*)

No.	First author, year	Study design	Age	Gender (M/F)	NF types	Anatomical location	Size (mm)	Ruptured (Y/N)	Presentation
40	Miura, 2005	CR	46	M	1	R 7th intercostal	6	Y	Back pain, collapse, hemothorax
41	Arai, 2007	CR	72	F	–	10th intercostal	–	Y	Chest pain, back pain, hemothorax
42	Arai, 2007	CR	49	M	–	11th intercostal	–	Y	Bain pain, dyspnoea, hemothorax
43	Matsumoto, 2007	CR	49	M	1	L 11th intercostal	30	Y	L back pain, dyspnoea, L massive pleural effusion, hemothorax
44	Ottinger, 2012	CR	46	M	1	R 9th intercostal	16	Y	R thoracic pain, dypsnoea, R hemothorax
45	Uzuka, 2012	CR	42	M	1	L 11th intercostal	42	N	L back pain
46	Misao, 2012	CR	40	M	1	R 10th intercostal and L 12th intercostal	18; 3	Y	First two 10th ICA aneurysms asymptomatic; sudden right back pain and dyspnoea following rupture of 12th ICA aneurysm
47	Hongsakul, 2013	CR	46	F	1	L 5th intercostal	8	Y	Pleuritic chest pain, dypsnoea
48	Puyanesarajah, 2015	CR	32	M	1	L 5th intercostal	–	N	Thoracic back pain, myelopathic symptoms due to spinal cord compression from intercostal arterial aneurysm
49	Kown, 2016	CR	50	M	1	R IMA	–	Y	Dypsnoea, hemothorax
Visceral artery aneurysms (n = 8)									
50	Hassen-Khodia, 1997	CR	55	F	1	SMA and hepatic artery	40; 15	N	RLQ pain; tender pulsatile SOL in RLQ – aortography identified 2 saccular aneurysms
51	Mendonca, 2010	CR	31	F	1	2 × SMA	25;17	Y	Hypotension, abdominal pain
52	Mendonca, 2010	CR	31	F	1	SMA	–	N	Leak in previously stented aneurysm
53	Somarouthu, 2011	CR	27	F	1	L RA	9	N	Hypertension, renal artery stenosis
54	Triantafyllidi, 2012	CR	28	F	1	2 × L RA	–	N	Headache, hypertension
55	Morris, 2013	CR	14	M	1	R hepatic and common hepatic arteries	50 (RHA); 20 (CHA)	N	Jaundice, nausea, vomiting. Right sided abdominal mass from right costal margin to pelvis.
56	Niwa, 2013	CR	41	F	1	2 X L RA	7; 8	Y	Hypotension, L flank pain, costovertebral tenderness
57	Im, 2015	CR	43	M	1	Gastroduodenal artery and R RA	–	Y	Haematosis and haemorrhagic shock
Others (n = 9)									
58	Scheuerlein, 2009	CR	69	F	1	R ulnar artery	13	Y	R arm swelling and numbness; impaired movement of fingers
59	Zhang, 2010	CR	62	M	1	R internal pudendal artery	80	Y	Sudden pain and enlarging mass in perineum and scrotum
60	Park, 2012	CR	49	M	1	Infrarenal aorta aneurysm, L common iliac artery	30; 70	Y	Mid-abdominal pain and lower back pain, gross haematuria
61	Hori, 2012	CR	78	M	1	Infrarenal aorta	55	N	Nil
62	Choong, 2012	CR	30	M	1	L internal iliac artery and PFA	–	Y	Ongoing haemorrhage from stump site following above-knee amputation
63	Hamasaki, 2014	CR	63	F	1	L internal thoracic artery	–	Y	L neck pain and swelling
64	Moreau, 2014	CR	74	F	1	L subscapular artery	10	Y	L pectoral pain and axillary mass
65	Yow, 2015	CR	55	F	1	Superior rectal artery	–	Y	Abdominal pain, diarrhoea, hypotension
66	Seinturier, 2016	CR	–	–	1	Femoral vein	–	N	Pulmonary embolism

Abbreviations
CA – Cervical artery.
ECA – External carotid artery.
ICA – Internal carotid artery.
IMA – Internal mammary artery.
MMA – Middle meningeal artery.
MCA – Middle cerebral artery.
RA – Renal artery.
SMA – Superior mesenteric artery.
SCA – Subclavian artery.
TCA – Thyrocervical artery.
VA – Vertebral artery.

large-size vessels and is estimated to affect between 0.4–6.4% of all patients [3–5]. The most common clinical manifestation of vascular disease in neurofibromatosis early-onset hypertension secondary to renal artery stenosis [3–5]. Common sites of aneurysm formation in this population include the aorta, renal arteries, mesenteric arteries, carotid and vertebral arteries and cerebrovascular system [1,2]. Vascular disease is the second most common cause of mortality in neurofibromatosis type 1 after malignancy [6].

Aneurysms in neurofibromatosis patients are frequently asymptomatic [3–5] with patients often presenting following rupture of an undiagnosed lesion. Management options include medical management of coexisting hypertension and modification of cardiovascular risk factors. Surgical intervention is guided by the age and comorbidities of the patient as well as the site and type of aneurysm. Options include open aneurysmectomy with or without arterial reconstruction using autologous or biosynthetic grafts, bypass grafting or endovascular repair [7]. Endovascular aneurysm repair techniques described in the literature include coil or acrylic glue embolization, stent grafts and intravascular detachable balloons (Table 1).

We systematically reviewed all existing reports of the endovascular management of neurofibromatosis aneurysms. To our knowledge this is the most up-to-date and comprehensive appraisal of the published literature regarding current endovascular management of aneurysms in neurofibromatosis patients.

2. Materials and methods

2.1. Literature search

This systematic review followed quality reporting guidelines set by PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) group [8]. An electronic search was carried out using Medline, Embase and Cochrane database records from 1946 to August 2017. The search terms “neurofibromatosis”, “Recklinghausen”, “aneurysm”, “pseudoaneurysm”, “emboli*”, “stent*”, “stent”, “coil*”, “coil”, “balloon” and “endovascular” were used as described in the electronic search strategy. No date or language restrictions were made. The latest date for this search was 31st August 2017.

2.2. Inclusion criteria for review

We included any article that reported the use of endovascular surgery to treat aneurysms in patients with neurofibromatosis. Both aneurysms and pseudoaneurysms associated with neurofibromatosis were included. Any coiling, stenting and balloon angioplasty procedures were considered to be endovascular surgical procedures and included. Articles were classified according to study type.

2.3. Exclusion criteria for review

Laboratory and animal studies were excluded. Articles discussing endovascular repair of aneurysms in patients without a confirmed diagnosis of neurofibromatosis and those that included an open surgical technique for aneurysm repair were excluded. Where patient data was duplicated in different publications, the older and/or smaller dataset was rejected.

2.4. Data extraction and validation of studies

Five reviewers (DB, MMV, IW, KW, AC) undertook independent reviews of the title, abstract and full text of extracted articles, and identified relevant articles by consensus. If disputed, AC would be the arbiter to resolve differences of opinions. DB and KW independently extracted the following data from each included study using a pre-determined datasheet. The following variable were recorded: study type, first author, year of publication, number of subjects, study population characteristics, pathology, vasculopathy type, size of lesion, rupture status, endovascular treatment method and materials, treatment outcome and follow up. Studies in other languages were translated into English by native speakers. The reviewers then extracted relevant data using the original document, the English abstract and our translation. The outcomes of interest are: 30-day mortality, post-operative complications, and follow-up outcomes.

2.5. Data analysis

As there were no prospectively controlled trials in our study, the Cochrane risk of bias assessment tool was not utilized to qualitatively examine the risks of bias [9]. Furthermore, due to missing data, and data heterogeneity, a meta-analysis was not performed. Data was presented as mean ± standard deviation. A systematic review was therefore undertaken using the quality reporting guidelines set by PRISMA guidelines.

3. Results

Our systematic search revealed a total of 220 publications for possible inclusion. Duplicate publications were excluded leaving 154 publications for review. On the basis of title and abstract review, irrelevant publications or those not fitting our inclusion criteria were excluded. Of these, 78 publications were assessed in their entirety and from these 19 publications were excluded due to 1. Insufficient data presented (n = 8), 2. Open intervention described (n = 5), 3. No intervention described (n = 3), 4. Review article (n = 2) 5. No original data (n = 1). All included articles (n = 59) were case reports and therefore received a SIGN grading of 3 following quality assessment [10]. Details of the search strategy are shown in Fig. 1.

3.1. Clinical presentation

Demographic information is provided in Table 1. Of 66 included patients, 35 are female (57%). The mean age at presentation was 44.3 ± 30 years (mean ± SD). Of patients described, 59/66 (89%) had neurofibromatosis type 1, one had neurofibromatosis type 2 and six reports did not classify the subtype of neurofibromatosis.

Patients presented either following aneurysm rupture (n = 42, 63.6%) or with an intact aneurysm with or without accompanying signs or symptoms (n = 22 [33.3%] and n = 2 [3.1%], respectively). Those with a ruptured aneurysm had an acute presentation, often with hemodynamic instability and/or loss of consciousness with localised pain and swelling due to an expanding haematoma. Cases with an intact aneurysm either presented as a mass with compressive symptoms (including hoarseness, dysphagia, vascular insufficiency, limb weakness and sensory symptoms) or were asymptomatic and detected by screening computed tomography.

3.2. Aneurysm features

Amongst the 66 patients with aneurysms who undergone endovascular repair, 3/66 (4.5%) suffered from intracranial aneurysms; 8/66 (12.1%) suffered from visceral artery aneurysms (including hepatic, superior mesenteric, gastroduodenal and renal arteries), and other patients suffered from aneurysms within the chest, abdomen, pelvis, upper limbs and neck (see Table 1 for details) [11]. Pseudoaneurysms were repaired in 10/66 (15.2%) of case reports. Ten (15.2%) patients had two or more aneurysms at presentation, these were located in the occipital (n = 1), vertebral (n = 1), neck (n = 1), intercostal (n = 1), iliac (n = 1) and visceral arteries (n = 5; hepatic [n = 2], renal [n = 2] and superior mesenteric arteries [n = 1]).

Lesion size was reported in 31/66 (47%) of cases. The median size of ruptured aneurysms was 13 mm (range 3 mm to 80), which was smaller than the median size of symptomatic aneurysms (25 mm, range

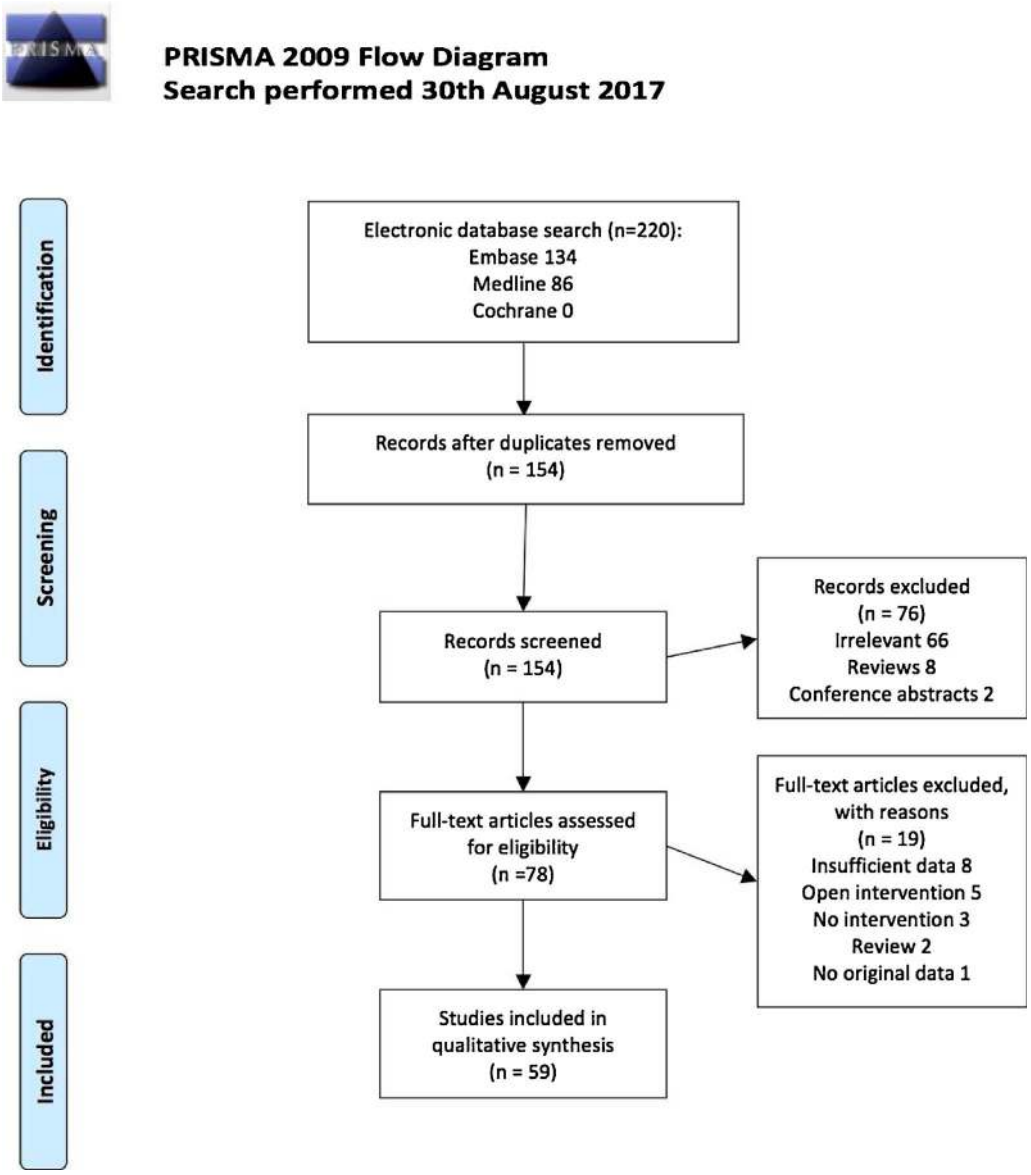

Fig. 1. PRISMA flow diagram of search strategy.

4 mm to 55 mm). Unfortunately, the sizes of asymptomatic aneurysms were not reported.

The majority of patients with aneurysms and pseudoaneurysms affected left-sided vessels (n = 44, 56.4%), with the remaining affected right-sided (n = 25, 32.1%) and 'central' vessels (e.g. aorta, SMA; n = 9, 11.5%).

3.3. Endovascular procedures

There were four main endovascular procedures described to treat aneurysms and pseudoaneurysms – coiling, stenting, balloon placement and embolisation with *n*-Butyl-cyanoacrylate (NBCA) glue. Coiling was the most commonly used technique, described in 55/66 (83.3%) cases. A variety of coil types were used, including – bare platinum, coated metal, biologically active (e.g. hydrogel-coated) and detachable. There was invariably a variety of grafts employed. There were 12 (18.2%) covered stents deployed in 10 patients [12–20], of which two (3%) were self-expandable covered graft [20,21]; 7 (10.6%) were balloon-expandable; and 3 were not mentioned by the authors. The balloon detachable technique was performed in four patients (6.1%) [22–25] (Table 2).

3.4. Outcomes

Details regarding procedure success and complications, though reported in all case reports, were limited. Complications were classified as either minor (nominal therapy with no consequence) or major (death; major therapy; hospitalization longer than 24 h) in accordance to the guidelines by the Society of Interventional Radiology [26]. We further classify the recurrence of similar lesion as a "technical failure", and persistence of signs and symptoms as "clinical failure". There were 10 incidences (15%) of major complications, of which 4 (6%) were attributed to perioperative death. Amongst these 4 deaths, one died 4 days post-operatively due to bleeding from left cervical hematoma leading to large hemothorax and cardiac arrest [27]; one suffered from hypoxic encephalopathy with evidence of spotty cerebellar infarcts caused by microthrombi secondary to vertebral artery embolization [28]; one died due to pulmonary oedema from excess colloid resuscitation whilst bleeding [15]; and one died due to vertebral artery dissection [29]. The 6 (9.1%) other incidences of major complications were due to technical failures arising from recurrent aneurysms. One patient had aneurysmal revascularization of the left vertebral artery, which warranted surgical aneurysmorrhaphy with thrombectomy [30]. One patient had a recurrence of intercostal aneurysm 5 days

Table 2
Technical procedures and endovascular outcomes.

No.	First author, year	Coils	Stent graft	Other techniques	Minor complications	Major complications	Technical failure	Clinical failure	Follow-up
Total (n = 66)		–	7 balloon-expandable; 2 self-expandable; 3 not mentioned	4 detachable balloon	4 (6%)	10 (15%)	6 (9.1%)	3 (4.5%)	–
Intracranial aneurysms									
1	Lesley, 2004	4:1 mixture of iodized oil (Cordis Neurovascular) and NBCA (Cordis Neurovascular) with added tantalum powder (Cordis Neurovascular)	0		0	0	0	0	–
2	Ellis, 2011	3 platinum coils	0		0	0	0	0	11
3	Kanematsu, 2011	4 DCS, IDC-18 (Boston Scientific), 8 FPC, Tornado Embolization coils (Cook Medical Inc.)	0		0	0	0	0	28
Neck artery aneurysms									
4	Teitelbaum, 1998	DCS and FPC (Target Therapeutics, Fremont, CA)	0		0	0	0	0	2 and 8
5	Smith, 2000	5-mm Gianturco coil and 8-mm Gianturco coil	2 PTFE-covered balloon expandable stents in internal carotid – Palmaz 394 and Palmaz 204		0	0	0	0	6 and 18
6	Arai, 2007	Microcoils	0		0	0	0	0	–
7	Sun, 2007	NBCA	0		0	0	0	0	–
8	Ku, 2008	MicroCoils	Stent graft in the right ECA, bridging the orifice of the right ICA to exclude internal carotid flow		0	0	0	0	–
9	Chovanec, 2009	–	–		0	0	0	0	3
10	Kanematsu, 2011	DCS (4-mm diameter/10-cm length; IDC-18; Boston Scientific) and FPC (one 4/2-mm, and seven 3/2-mm coils; Tornado Embolization Coils; Cook Medical Inc.)	0		0	0	0	0	6
11	Moratti, 2012	Hydrocoils, IDC-18 (Boston Scientific)	0		1	0	0	1	6,20,30
12	Hung, 2012	Metallic coil	0		0	0	0	0	–
13	Anpalakhan, 2013	–	–		0	0	0	0	–
14	Hamasaki, 2014	Axium DCS (ev3 Covidien, Irvine, California)	0		0	0	0	0	6
15	Hoonjan, 2014	Microcoils	0		0	1	0	0	–
16	Lee, 2015	DCS	0		0	0	0	0	–
17	Leclerc, 2017	0	6 × 100 mm non-heparin-bonded, covered balloon expandable stent graft (Viabahn, WL Gore & Associates Inc.)		0	0	0	0	12
Vertebral artery aneurysms									
18	Negoro, 1990	0		Detachable balloon	0	0	0	0	5
19	Muhonen, 1991	0		Detachable balloon	0	0	0	0	1.5
20	Ushikoshi, 1999	0		Detachable balloon	0	0	0	0	–
21	Horsley, 1997	Hilal microcoils	0		0	0	0	0	24
22	Roth, 2000	Coil + n-nutyl cyanoacrylate + ethiodized oil embolization	0		0	0	0	0	6
23	Hidea, 2007	DCS (IDC; Boston Scientific, Target Therapeutics) and microcoils (Tornado Embolization Coils, Cook, Bloomington, IN)	0		0	1	0	0	–
24	Hiramatsu, 2007	DCS	0		0	0	0	0	–
25	Peyre, 2007	DCS 18 (Boston Scientific, Natick, MA; Target, Fremont, CA)	0		1	0	0	1	72
26	Horie, 2008	DCS 18 (Boston Scientific, Natick, MA; Target, Fremont, CA)		Detachable balloon	0	0	0	0	–
27	Sandhu, 2008	2 × 3 mm microcoils	10 mm covered balloon expandable JoStent (JoMed)		0	1	0	0	–
28	Higa, 2010	Multiple coils	0		0	0	0	0	36

(*continued on next page*)

Table 2 (*continued*)

No.	First author, year	Coils	Stent graft	Other techniques	Minor complications	Major complications	Technical failure	Clinical failure	Follow-up
Total (n = 66)		–	7 balloon-expandable; 2 self-expandable; 3 not mentioned	4 detachable balloon	4 (6%)	10 (15%)	6 (9.1%)	3 (4.5%)	–
29	Hiramatsu, 2012	DCS (GDC18 Soft &18 Standard [Boston Scientific, Natick, Massachusetts, USA], DETACH-18 [Cook Medical Technologies, Bloomington, Indiana, USA], and Tornado fibered coils [Cook Medical Technologies])	0		0	0	0	0	–
30	Anpalakhan, 2013	Coil	0		0	0	0	0	–
31	Hamasaki, 2014	Axium DCS (ev3 Covidien, Irvine, California)	0		0	0	0	0	6
32	Uneda, 2016	10 Target XL DCS (Stryker), and 5 Orbit Galaxy DCS (Codman)	0		0	0	0	0	3
33	Strambo, 2017	3 Guglielmi DCS (GDC) 18-vortX® and 3 GDC-10 360	0		0	1	1	0	72
Subclavian artery aneurysms									
34	Kim, 2005	Tornado microcoil (Cook Europe, Bjaeverskov, Denmark) and two spiral coils (Balt, Montmorency, France)	0		0	0	0	0	2
35	Sakamoto, 2009	10 × 20 mm Wallstent RP (Boston Scientific, Natick, MA) and two DCS [Micrus CASHMERE (9 × 22 mm) and Micrus CASHMERE (7 × 17 mm); Micrus, San Jose, CA]	0		0	0	0	0	3
36	Mydin, 2015	0	0.9 × 5 cm covered balloon expandable Gore Viabahn stent graft		1	0	0	0	0
Intercostal artery aneurysms									
37	Kipfer, 2001	FPC (Vortexw fibered platinium coil-18, Boston Scientific/Target, Galway, Ireland)	0		0	0	0	0	–
38	Dominguez, 2002	6/300 FPC (Balt, Montmorency, France) and one 35/6-3 "Tornado" coil (Cook Europe, Bjaeverskov, Denmark)	0		0	0	0	0	19
39	Chang, 2005	5 mm coil (Occluding Spring Emboli, Cook, Bloomington, IN, USA)	0		0	0	0	0	10
40	Miura, 2005	7 FPC and one DCS	0		0	0	0	0	0
41	Arai, 2007	Microcoils	0		0	0	0	0	–
42	Arai, 2007	Microcoils	0		0	0	0	0	–
43	Matsumoto, 2007	Tornado Embolization Microcoils (Cook Incorporated, Minnesota, MN, USA) and a Trufill Pushable Coil (Johnson & Johnson Cordis endovascular system, Miami, FL, USA)	0		0	1	1	0	12
44	Ottinger, 2012	48 Fibercoils with diameter 3.5–6 mm (Boston Scientific, Cork, Ireland)	0		0	1	1	0	2
45	Uzuka, 2012	DCS (Boston Scientific)	0		0	0	0	0	–
46	Misao, 2012	6 microcoils (Tornado; Cook, MN, USA); 3 microcoils (Tornado) and 2 DCS (Detach; Cook).	0		0	0	0	0	–
47	Hongsakul, 2013	FPC (4 mm–2 cm, Diamond-18, Boston-Scientific, Cork, Ireland)	0		0	0	0	0	12
48	Puyanesarajah, 2015	Coil	0		0	0	0	0	36
49	Kown, 2016	two 5-mm Tornado Embolization Microcoils (Cook Medical INC. IN, Bloomington, USA)	0		0	1	0	1	6
Visceral artery aneurysms									
50	Hassen-Khodia, 1997	Microcoil (Cook Co., Bloomington, Ind.)	0		0	0	0	0	24
51	Mendonca, 2010	0	PTFE-covered balloon expandable stent (Advanta V12, 6 38 mm, Atrium Medical Corporation, Hudson, NH)		0	0	0	0	6
52	Mendonca, 2010	Microcoils	0		0	0	0	0	–
53	Somarouthu, 2011	DCS (Helipaq coils, Micrus Endovascular, San Jose, California)	Self-expandable stent (4 × 20, Xpert, Abbott Laboratories, Illinois)		0	0	0	0	18
54	Triantafyllidi, 2012	Microcoils	2 × covered stents		1	0	0	1	–
55	Morris, 2013	6-mm microcoils (Cook Medical Inc., Bloomington, IN)	0		0	0	0	0	–
56	Niwa, 2013	FPC (Vortex; Boston Scientific, Cedex, France)	0		0	0	0	0	–

(*continued on next page*)

Table 2 (*continued*)

No.	First author, year	Coils	Stent graft	Other techniques	Minor complications	Major complications	Technical failure	Clinical failure	Follow-up
Total (n = 66)		–	7 balloon-expandable; 2 self-expandable; 3 not mentioned	4 detachable balloon	4 (6%)	10 (15%)	6 (9.1%)	3 (4.5%)	–
57	Im, 2015	Microcoils (Nester Embolization Microcoil; Cook Medical,Bloomington, IN, USA)	0		0	0	0	0	–
Others									
58	Scheuerlein, 2009	Guglielmi DCS (GDC, Target Therapeutics/Boston Scientific, Fremont, Calif)	0		0	0	0	0	3
59	Zhang, 2010	Spiral coils (Cook)	0		0	0	0	0	6
60	Park, 2012	0	SEAL device (S&G Biotech Inc., Seongnam, Korea) – Covered balloon expandable stent graft		0	1	1	0	–
61	Hori, 2012	0	Powerlink stent graft (Endologix, Irvine, CA, USA) – Covered self-expandable stent graft		0	1	1	0	–
62	Choong, 2012	Microcoils	0		0	0	0	0	–
63	Hamasaki, 2014	Microcoils	0		0	0	0	0	6
64	Moreau, 2014	Microcoils (Tornado™ Embolization Microcoils, Cook Europe, Bjaeverskov, Denmark)	0		0	0	0	0	–
65	Yow, 2015	Microcoils	0		0	1	1	0	–
66	Seinturier, 2016	–	–		0	0	0	0	–

Abbreviations
DCS – Detachable coil system.
FPC – Fiber Platinum coils.

postoperative, and was successfully treated with Tornado Embolization Microcoils [31]. One other patient succumbed to right-sided hematoma but was safely evacuated by thoracotomy. Three other patients [19,20,32] suffered from aneurysmal recurrence, and were all treated successfully with either open surgeries or laparotomies. The rates of minor complications (6%) and clinical failure (4.5%) were low. One patient continued to suffered moderate dysphagia 6 months post-procedure, but resolved spontaneously [33]. One patient had persistent radicular pain with fluctuating intensity postoperatively [34]. Although one patient suffered from a potentially risky extrapleural hematoma, no intervention was undertaken as the bleeding stopped spontaneously [16]. One other patient suffered from persistent hypertension and impaired left kidney function 1 month postoperatively, but declined any interventions [18]. In patients who survived with no minor or major perioperative complications, discharge details were reported in 18/62 (29%) cases with an average time to discharge post-procedure of 9.8 days (range: 2–28 days). A follow-up period was reported in 32/62 (51.6%) cases, with the average last follow-up appointment 15 months (range: 1.5–72 months) post- procedure. Albeit not procedural-related complications, two patients developed another vascular lesion distant from the treated lesion(patients 18 and 42) [24,29]. A summary of endovascular outcomes is detailed in Table 2.

4. Discussion

Neurofibromatosis is an autosomal dominant genetic disorder, involving hamartomatous proliferation of neoplastic cells of the central and peripheral nervous system. It affects the brain, spinal cord, skin, eyes, and long bones [12]. Although rare, neurofibromatosis (NF) is also associated with a number of vascular abnormalities of medium and large-sized arteries, including aneurysms. Although it commonly involves a few vessels, most patients are asymptomatic. Mechanistically, vasculopathy in NF patients can be attributed to the alteration of neurofibromin, which is expressed in endothelial and smooth muscle cells [3–5]. In 1945, Reubi first described three main types of arterial lesions in small vessels less than 1 mm in diameter, largely in the kidney. These involved intimal thickening causing lumen occlusion, fragmentation of muscularis and elastic causing vessel wall dilatation, followed by fusocellular nodularity that weakens the integrity of the vessel wall [35]. Several alternative theories were later proposed, which included proliferation of Schwann cells within vessel wall, causing degenerative changes [36]; neurofibromatous or ganglioneuromatous tissue changes association large vessels; vessel dysplasia associated with smaller vessels [37].

This findings from this review showed that rupture of aneurysm is a rather common phenomenom (63.6%). Aneurysms commonly present in unusual locations, which can lead to fatal consequences after a rupture. Leier and colleagues proposed two hypotheses for the causes of arterial rupture: 1) weakening of the vessel wall due to neurofibromatous invasion of the tunica media; 2) compression of the vasa vasorum of the large artery by neurofibromatous tissue, weakening an arterial segment [38]. However, as aneurysms are largely symptomatic, it is not a significant challenge to identify patients at risk of rupture. As evident from this review, a significant (33.3%) proportion of patients with intact aneurysms were largely symptomatic; they were detected either from symptoms such as a mass or hoarseness, or accidental findings on images. Unless they are detected early, these patients are at significant risk of suffering from a rupture and its adverse consequences.

The findings from this review would suggest that middle-aged adults with neurofibromatosis type 1 (NF-1) are at particular risk of developing aneurysms. NF-1 patients suffer from variable clinical manifestations. Vasculopathy, hypertension and congenital cardiovascular malformation are the three most common cardiovascular manifestations [39]. In particular, NF-1 vasculopathy commonly includes aneurysms, stenosis, and arteriovenous deformities [2]. Although the findings from this review does not support aneurysm location as a risk factor, Oderich and colleagues demonstrated that symptomatic vasculopathy most commonly affects the renal arteries (40.3%), and tend to be stenotic instead of aneurysmal [2]. The latter is in agreement with our evidence, where 3 out of the 4 cases involving the renal arteries showed stenotic symptoms rather than aneurysmal. In addition, only 1 patient suffered from a renal artery rupture. Since the median aneurysmal size of rupturex aneurysms was smaller than the size of symptomatic aneurysms, it seems to suggest that aneurysm size is not a risk factor for rupture.

The assemblage of case reports in this review appear to support the use of endovascular repair even in hemodynamically unstable patients at all ages. In addition, given the low 30-day mortality rate, minor complication and clinical failure rates, it appears to be a safe approach for NF patients with aneurysm. However, endovascular management can be challenging at times; surgeons should be ready to consider open surgery if the patient displays persistent signs of bleeding and other symptoms [32].

Although there are currently no standard recommendations for a vascular workup in NF patients, the vascular tree should be screened selectively to detect early aneurysmal or stenotic changes in patients deemed clinically suspicious. Although reconstructed three-dimensional angiography is able to display the anatomy of the vasculature, it is not effective in identifying the bleeding source. Dynamic contrast-enhanced multidetector computer tomography, on the other hand, may be a more useful tool [40]. As patients may present with multiple lesions, it is suitable to conduct imaging studies of the head, chest, and abdominal regions. However, the rarity of clinically significant lesions (2%) might be a challenge for clinicians to conduct regular vascular assessments for all NF patients [2].

4.1. Limitations

The evidence presented in this review is limited by the risk of bias of included studies, which is composed of only case reports, with no randomized controlled trials. In this regard, we were only able analyze the data with crude statistics, without conducting a formal meta-analysis.

4.2. Implications for research

Given the paucity of data, it will be up to individual institutions and surgeons to develop their own protocol and guidelines. Moreover, it will be unethical to conduct randomized clinical trials, where patients with high-risk ruptured aneurysms are randomized to a treatment arm, or patients with asymptomatic aneurysm are randomized to undergo open surgical procedures. The panacea of treatment depends very much on the individual patient's clinical situation. Hence, researchers should consider other study designs, such as consolidating a large case series or retrospective analyses, to address the paucity of data.

5. Conclusions

Albeit rare, patients with neurofibroblastoma suffer from a wide spectrum of complications, including vasculopathy. This can manifest either as an aneurysm or stenosis, both of which have severe clinical manifestations and fatal consequences. Endovascular management of these patients is safe and effective even in hemodynamically unstable patients at all ages.

Disclosures

Financial support: no grants or funding have been received for this study.

Conflicts of interest

All authors have no conflicts of interest to declare.

References

[1] K.T. Delis, P. Gloviczki, Neurofibromatosis type 1: from presentation and diagnosis to vascular and endovascular therapy, Perspect. Vasc. Surg. Endovasc. Ther. 18 (3) (2006) 226–237.

[2] G.S. Oderich, T.M. Sullivan, T.C. Bower, P. Gloviczki, D.V. Miller, D. Babovic-Vuksanovic, et al., Vascular abnormalities in patients with neurofibromatosis syndrome type I: clinical spectrum, management, and results, J. Vasc. Surg. 46 (3) (2007) 475–484.

[3] A.E. Lin, P.H. Birch, B.R. Korf, R. Tenconi, M. Niimura, M. Poyhonen, et al., Cardiovascular malformations and other cardiovascular abnormalities in neurofibromatosis 1, Am. J. Med. Genet. 95 (2) (2000) 108–117.

[4] S.J. Hamilton, J.M. Friedman, Insights into the pathogenesis of neurofibromatosis 1 vasculopathy, Clin. Genet. 58 (5) (2000) 341–344.

[5] J.M. Friedman, J. Arbiser, J.A. Epstein, D.H. Gutmann, S.J. Huot, A.E. Lin, et al., Cardiovascular disease in neurofibromatosis 1: report of the NF1 cardiovascular task force, Genet. Med.: Off. J. Am. Coll. Med. Genet. 4 (3) (2002) 105–111.

[6] S.A. Rasmussen, Q. Yang, J.M. Friedman, Mortality in neurofibromatosis 1: an analysis using U.S. death certificates, Am. J. Hum. Genet. 68 (5) (2001) 1110–1118.

[7] S. Tatebe, F. Asami, H. Shinohara, T. Okamoto, S. Kuraoka, Ruptured aneurysm of the subclavian artery in a patient with von Recklinghausen's disease, Circ. J.: Off. J. Jpn. Circul. Soc. 69 (4) (2005) 503–506.

[8] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Ann. Intern. Med. 151 (4) (2009) 264–269 w64.

[9] J.P. Higgins, D.G. Altman, P.C. Gotzsche, P. Juni, D. Moher, A.D. Oxman, et al., The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, BMJ (Clin. Res. ed). 343 (2011) d5928.

[10] R. Harbour, J. Miller, A new system for grading recommendations in evidence based guidelines, BMJ: Br. Med. J. 323 (7308) (2001) 334–336.

[11] C. Seinturier, S. Blaise, F. Thony, J.L. Magne, G. Pernod, A femoral common vein aneurysm in a patient with neurofibromatosis syndrome type 1, Ann. Vasc. Surg. 40 (299) (2017) e7–e9.

[12] B.L. Smith, C.E. Munschauer, N. Diamond, F. Rivera, Ruptured internal carotid aneurysm resulting from neurofibromatosis: treatment with intraluminal stent graft, J. Vasc. Surg. 32 (4) (2000) 824–828.

[13] Y.K. Ku, H.W. Chen, H.W. Chen, C.J. Fu, S.C. Chin, Y.C. Liu, Giant extracranial aneurysms of both internal carotid arteries with aberrant jugular veins in a patient with neurofibromatosis type 1, AJNR Am. J. Neuroradiol. 29 (9) (2008) 1750–1752.

[14] B. Leclerc, S. Rinckenbach, Endovascular repair with cervical access to treat a symptomatic internal carotid artery aneurysm in a patient with neurofibromatosis type 1, Eur. J. Vasc. Endovasc. Surg.: Off. J. Eur. Soc. Vasc. Surg. 53 (3) (2017) 402.

[15] C. Sandhu, T. Sabharwal, Spontaneous hemothorax in patients with neurofibromatosis treated with percutaneous embolization, Cardiovasc. Intervent. Radiol. 31 (6) (2008) 1260–1261.

[16] M.I. Mydin, A. Sharma, Z. Zia, M. Hawari, M. Jadoon, A. Majewski, A novel approach in managing right-sided haemothorax in neurofibromatosis type 1, Asian Cardiovasc. Thorac. Ann. 23 (5) (2015) 573–575.

[17] C.T. Mendonca, Regarding endovascular treatment of contained rupture of a superior mesenteric artery aneurysm resulting from neurofibromatosis type I, J. Vasc. Surg. 52 (5) (2017) 1425.

[18] H. Triantafyllidi, J. Papadakis, E. Brountzos, C. Arvaniti, K. Theodoropoulos, I. Panayiotides, et al., Neurofibromatosis type 1 and renal artery aneurysms: an uncommon entity of severe hypertension, Hellenic J. Cardiol.: HJC = Hellenike kardiologike epitheorese 53 (1) (2012) 80–86.

[19] Y.J. Park, K.M. Park, J. Oh, H.S. Park, J.S. Kim, Y.W. Kim, Spontaneous aortic rupture in a patient with neurofibromatosis type 1, J. Korean Surg. Soc. 82 (4) (2012) 261–265.

[20] D. Hori, K. Yuri, K. Nemoto, A. Yamaguchi, H. Adachi, Early aortic endograft failure in the presence of periaortic lymphadenopathy with neurofibromatosis (von Recklinghausen's disease), Gen. Thorac. Cardiovasc. Surg. 60 (5) (2012) 308–311.

[21] B. Somarouthu, J. Rabinov, W. Waichi, S.P. Kalva, Stent-assisted coil embolization of an intraparenchymal renal artery aneurysm in a patient with neurofibromatosis, Vasc. Endovasc. Surg. 45 (4) (2017) 368–371.

[22] N. Horie, M. Morikawa, N. Kitagawa, M. Nakamoto, I. Nagata, Successful endovascular occlusion of an aneurysm of the cervical vertebral artery associated with neurofibromatosis-1, Acta Neurochir. (Wien) 150 (8) (2008) 847–848.

[23] S. Ushikoshi, K. Goto, K. Uda, N. Ogata, Y. Takeno, Vertebral arteriovenous fistula that developed in the same place as a previous ruptured aneurysm: a case report, Surg. Neurol. 51 (2) (1999) 168–173.

[24] M. Negoro, T. Nakaya, K. Terashima, K. Sugita, Extracranial vertebral artery aneurysm with neurofibromatosis: endovascular treatment by detachable balloon, Neuroradiology 31 (6) (1990) 533–536.

[25] M.G. Muhonen, J.C. Godersky, J.C. VanGilder, Cerebral aneurysms associated with neurofibromatosis, Surg. Neurol. 36 (6) (1991) 470–475.

[26] T.G. Walker, S.P. Kalva, K. Yeddula, S. Wicky, S. Kundu, P. Drescher, et al., Clinical practice guidelines for endovascular abdominal aortic aneurysm repair: written by the Standards of Practice Committee for the Society of Interventional Radiology and endorsed by the Cardiovascular and Interventional Radiological Society of Europe and the Canadian Interventional Radiology Association, J. Vasc. Interventional Radiol.: JVIR 21 (11) (2010) 1632–1655.

[27] B. Hoonjan, N. Thayur, A. Abu-Own, Aneurysmal rupture of the costo-cervical trunk in a patient with neurofibromatosis type 1: a case report, Int. J. Surg. Case Rep. 5 (2) (2014) 100–103.

[28] M. Hieda, N. Toyota, H. Kakizawa, N. Hirai, T. Tachikake, Y. Yahiro, et al., Endovascular therapy for massive haemothorax caused by ruptured extracranial vertebral artery aneurysm with neurofibromatosis Type 1, Br. J. Radiol. 80 (952) (2007) e81–4.

[29] K. Arai, J. Sanada, A. Kurozumi, T. Watanabe, O. Matsui, Spontaneous hemothorax in neurofibromatosis treated with percutaneous embolization, Cardiovasc. Intervent. Radiol. 30 (3) (2007) 477–479.

[30] D. Strambo, L. Peruzzotti-Jametti, A. Semerano, G. Fanelli, F. Simionato, R. Chiesa, et al., Treatment challenges of a primary vertebral artery aneurysm causing recurrent ischemic strokes, Case Rep. Neurol. Med. 2017 (2017) 2571630.

[31] I. Matsumoto, Y. Ohta, Y. Tsunezuka, M. Tamura, M. Oda, G. Watanabe, Treatment for intercostal arterial aneurysm in neurofibromatosis type 1, Asian Cardiovasc. Thorac. Ann. 15 (1) (2007) e16–9.

[32] K.H. Yow, J. Bennett, P. Baptiste, P. Giordano, Successful combined management for ruptured superior rectal artery aneurysm in neurofibromatosis type 1, Ann. Vasc. Surg. 29 (6) (2015) e13–e16 1317.

[33] C. Moratti, T. Anderson, Giant extracranial aneurysm of the internal carotid artery in neurofibromatosis type 1: a case report and review of the literature, Interventional Neuroradiol. 18 (3) (2012) 341–347.

[34] M. Peyre, A. Ozanne, R. Bhangoo, V. Pereira, M. Tadie, P. Lasjaunias, et al., Pseudotumoral presentation of a cervical extracranial vertebral artery aneurysm in neurofibromatosis type 1: case report, Neurosurgery 61 (3) (2007) E658 discussion E.

[35] F. Reubi, Neurofibromatose et lesions vasculaires, Schweiz. Med. Wochenschr. 75 (1945) 463–465.

[36] W.R. Salyer, D.C. Salyer, Vascular lesions of neurofibomatosis, Angiology (1974) 510–519.

[37] J. Greene, J. Fitzwater, j. Burgess, Arterial lesions associated with neurofibromatosis, Am. J. Clin. Pathol. (1974) 481–487.

[38] C.V. Leier, C.J. DeWan, L.F. Anatasia, Fatal hemorrhage as a complication of neurofibromatosis, Vasc. Surg. 6 (2) (1972) 98–101.

[39] N. Niwa, H. Yanaihara, M. Horinaga, Y. Nakahira, F. Hanashima, H. Asakura, Spontaneous renal artery aneurysm rupture in a patient with neurofibromatosis type 1 without risk factors for renal artery aneurysm rupture, Vasc. Endovascular Surg. 47 (7) (2013) 558–560.

[40] T. Misao, T. Yoshikawa, M. Aoe, Y. Ueda, M. Yodoya, J. Sakurai, Recurrent rupture of intercostal artery aneurysms in neurofibromatosis type 1, Gen. Thorac. Cardiovasc. Surg. 60 (3) (2012) 179–182.