Case Report

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Vascular Complications of Neurofibromatosis Type 1–A Case Report and Literature Review with Special Emphasis on Pregnancy

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Abstract

Vascular involvement in Neurofibromatosis type 1 (NF1) may result in major hemorrhage due to the rupture of an affected vessel or during surgery for neurofibromas. Pregnancy in women with NF1 is characterized by disease specific and obstetric complications. These include an increase in number and size of neurofibromas, preeclampsia, placental abruption, fetal growth restriction, and preterm birth.

We present the case of a pregnant patient with NF1 who suffered a perioperative rupture of the left common iliac artery during her third cesarean section. To further investigate hemorrhagic complications in patients with NF1, and during pregnancy in particular, we performed a literature search. PubMed database was used covering the time between inception and October 2021. In all, 154 cases were included. With the exception of six these were single case reports. 143 non-obstetric cases were described (77 women (53%), 66 men (46%)). Median age was 45 years (IQR 36-53). Affected vessels were predominantly from the trunk (n=96, 67%), followed by head and neck (n=34, 24%) and limbs (n=13, 9%). Overall mortality was 21.6%, without difference between sex and location.

Reports of 11 pregnant or postpartum women were found. All antepartum incidents (n=4) occurred during the third trimester, and postpartum cases (n=7) within two weeks after delivery; three women (27.3%) died. Perinatal survival of cases with vessel ruptures during pregnancy was not reported (n=1), intrauterine fetal death (n=1), and survival (n=2) with poor and non-reported Apgar score, respectively.

Overall, 61 reports (39%) included histopathological findings. Elastin fragmentation, changes of the vessel wall structure, neurofibroma, or positive results for S-100 protein was commonly reported. Vessel ruptures in patients with NF1 are rare; the 21.6% mortality rate may be an underestimation. Female sex and the reproductive phase are overrepresented. The adverse association between pregnancy and NF1 may be attributable to the hormonal changes and the hyperdynamic cardiovascular state of pregnancy. Until now, screening and preventive measures of vascular complications in NF1 are not available. A high level of suspicion, immediate attention of a multidisciplinary team, with availability of large amounts of blood products are a prerequisite of successful treatment.

Keywords: Pregnancy complications; Pregnancy; Obstetrics; Neurofibromatosis type 1; Iliac artery; Ruptured aneurysm; Hemorrhage

Abbreviations: IQR; Interquartile range; N number; NF1, Neurofibromatosis type 1

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Introduction

Neurofibromatosis Type 1 (NF1, Mendelian Inheritance in Man #162200), is an autosomal dominant multisystem disease with an estimated prevalence of 1:3000 [1]. Located on 17q11.2, NF1 encodes neurofibromin, a tumor suppressor. The disease is characterized by a high phenotypic variability. Two or more of the following criteria need to be fulfilled: presence of more than six café-au-lait macules; two or more neurofibromas of any type or one plexiform neurofibroma; freckling in the axillary or inguinal regions; optic glioma; two or more Lisch nodules; a distinctive osseous lesion such as tibial pseudoarthrosis; or a first-degree

relative diagnosed by the above citeria [2-4].

Vascular involvement of NF1 includes arterial dysplasia, stenosis, occlusion, ectasia and aneurysm formation. Major hemorrhage may occur as a result of rupture of the affected vessel, or during surgery for neurofibromas [5-6].

Pregnancy in affected women is characterized by NF1-specific and obstetric complications. These include, among others, an increase in number and size of neurofibromas, preeclampsia, placental abruption, fetal growth restriction, and preterm birth [7-10].

We present the case of a pregnant patient with NF1 who suffered an iliac artery rupture. For further investigation of hemorrhagic complications in patients with NF1, and during pregnancy in particular, we performed a literature search.

Case Presentation

The patient's diagnosis was established during childhood. There was no other affected family member. A genetic analysis had been performed during infancy, which had not revealed a pathogenic mutation. Her most prominent manifestation was the presence of multiple neurofibromas predominantly of the left lower body; corrective osteotomy of the left femoral head with excision of a neurofibroma had been performed during childhood (Figure 1A, B). Her obstetric history is summarized in Table 1.

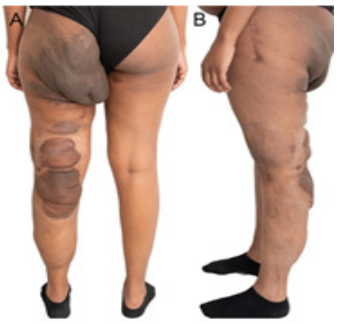

Figure 1: Picture of the lower body with neurofibroma posterior (A) and left lateral (B).

Table 1: Obstetric details, case report.

Pregnancy number/ maternal age	Complications during pregnancy	GA at delivery	Mode of delivery	Maternal complications postpartum	Fetal complications	Newborn data	Neonatal complications
18-Jan	Preterm labor, PROM, placental abruption	36+6	Emergency CS	Lymphatic swelling in the left lower limb	Uteroplacent al dysfunction	F, 2390 g (15. P.), Apgar 2/6/7, UA-pH 6.67	Asphyxia, adrenal hemorrhage
20-Feb	HELLP syndrome, placental abruption	36+4	CS	HELLP syndrome, AKI, ARDS, coagulopathy	Fresh stillbirth	M, 2900 g (41. P.)	n. a.
24-Mar	Preterm labor	35+2	CS	Cardiovascular arrest immediately after CS; CPR, relaparotomy, ROSC after 32 min.; hemoperitoneum due to spontaneous rupture left common iliac artery; reconstruction with bovine patchplasty, retroperitoneal packing, embolization left ovarian artery	none	M, 2400 g (26. P.), Apgar 7/8/9, UA-pH 7.31	RDS, icterus

AKI: Acute Kidney Injury; APGAR: Appearance, Pulse, Grimace, Activity, Respiration; ARDS: Adult Respiratory Distress Syndrome; CPR: Cardiopulmonary Resuscitation; CS: Cesarean Section; F: Female; GA: Gestational Age; HELLP: Hemolysis, Elevated Liver Enzymes, Low Platelets; M: Male; NA: Not Applicable; P: Percentile; PROM: Premature Rupture of Membranes; RDS: Respiratory Distress Syndrome; ROSC: Return Of Spontaneous Circulation; UA: Umbilical Artery

The histopathological examination of the iliac artery specimen revealed fibroid transformation of the vascular wall resulting in a disorganized structure of the smooth muscle cells (Figure 2).

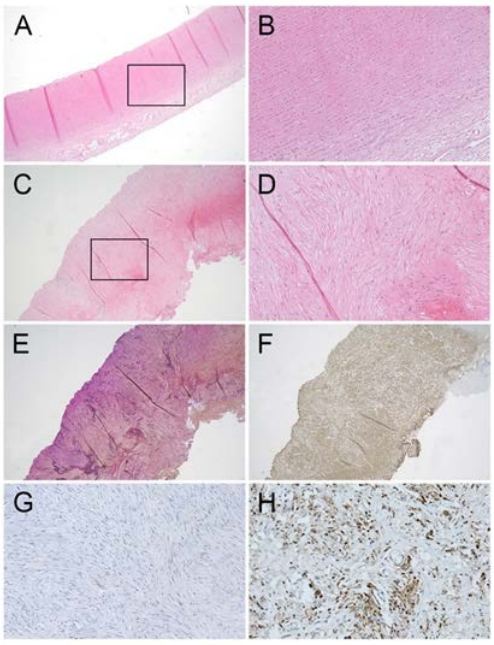

Figure 2: Histological sections of a normal arterial wall (A-B), of the ruptured iliac artery (C-G) and of the cutaneous neurofibroma from the presented patient (H): Normal arterial wall with regular structure (A, Hematoxylin-eosin-staining (HE), 40:1), with the magnification of the media (s. frame, A) showing parallel muscle cells and fibres (B, HE, 200:1). Wall of the iliac artery (C, HE, 40:1) with fibromuscular dysplasia and thickened wall showing distorted medial arrangement (D) in the magnification (HE, 200:1). The fragmentation of elastic fibres and proliferation of cellular elements are presented using Elastin van Gieson staining (E) and immunohistochemical staining of smooth muscle actin (F, both 40:1), respectively. Iliac artery without evidence of neurofibroma by a negative immunohistochemical staining of S 100 (G) in contrast to the staining in the cutaneous neurofibroma (H, both 200:1).

Methods

For literature research, the PubMed database was used covering the time between inception and October 2021. The following terms were applied: neurofibromatosis and pregnancy, neurofibromatosis and aneurysm, and neurofibromatosis and ruptured vessel. The title and abstract of the retrieved publications were read to assess the relevance. Additionally, references of publications were hand-searched for further reports. Study design and language were not restricted.

Results

A total of 913 citations was retrieved. After exclusion of duplicates and screening of titles and abstracts, 233 full-text articles were assessed; additionally, references were hand searched for further citations. Finally, 147 publications were included. With the exception of six publications, which reported on two or three cases each, these were single-case reports (Figure 3) [11-16].

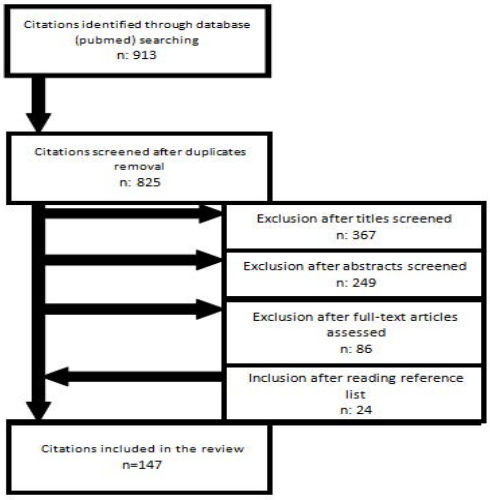

Figure 3: The selection process is depicted.

Non-obstetric cases were described in 137 reports (143 cases, in Table 1 supplementary), including 77 women (53%) and 66 men (46%), in supplementary Table 1. Median age was 45 (interquartile range (IQR) 36-53). Affected vessels were predominantly from the trunk (number (n)=96, 67%), followed by head and neck (n=34, 24%), and limbs (n=13, 9%). Treatment was successful in 108 of reported cases (76%) with survival of 77% for ruptures of trunk vessels, 73% for head and neck, and 69% for limb vessels. Outcome was not reported for four cases. Fatalities were equally distributed between women and men (15 and 16, respectively), corresponding to a 21.6% mortality rate.

Ten publications reported on 11 pregnant or postpartum women, see Table 2. Affected arteries were from the trunk (n=7), head and neck (n=3), and limb (n=1). All antepartum incidents (n=4) occurred during the third trimester, and postpartum cases within two weeks after delivery. Three women (27.3%) died. Perinatal survival of cases with vessel ruptures during pregnancy was not reported (n=1), intrauterine fetal death (n=1), and neonatal survival (n=2) with poor and non-reported Apgar score, respectively.

Table 2: Publications of vessel ruptures during pregnancy and postpartum in women with Neurofibromatosis Type 1.

Author	Age	GA /days pp	Affected artery	Treatment	Outcome		Period of hospitalization (days)	Country	Histopathology
					maternal	fetal			
Tateishi et al. 2019	42	28	Ascending aorta	CS; hysterectomy; ascending aorta replacement	survived	survived 1482 g	67	JP	Break in medial elastic fibers. Positive cells for S-100 protein in the media,
Hashimoto et al. 2021	39	34	L. intercostal causing hematothorax	CS; endovascular embolization	survived	n. r.	30	JP	no neurofibroma n. r.

Tidwell and Copas 1998	30	34	R. brachial	Initially venous replacement; transhumeral amputation after recurrence	survived	urvived2721 g APGAR 2/3/-s	30	US	Invasion of neurofibroma into the vessel wall
Tapp and Hickling 1969	35	35	R. renal	Resuscitation	died unop-erated	IUFT, IUFT, apparently normally developed fetus, 2400g	-	UK	Neurofibromatous thicken-ing
Brady and Bolan 1984	35	2	R. subcla-vian	-	died sur-vived	alive	-25	US US	Neurofibroma Fibrovascular tissue
	26	5	L. intercostal	Suture ligations		alive			
Serleth et al. 1998	20	3	Pancreati-coduodena l aneurysms	Embolization for unruptured aneurysms; laparotomy with ligation for ruptured aneurysms	survived	alive 1900g	54	US	n. r.
Narasimma n et al. 2019	33	4	R. intra-thoraci intercostal AVMs	R. thoracotomy; ligation and excision	survived	alive	30	MY	mesenchymal proliferative lesions, cells positive for S-100 protein, neurofibroma plexiforme
Sánchez-Contreras et al. 2020	36	7	L. common iliac	Laparotomies for recurrent ruptures; L. aortoiliac bypass	died	n. r.	n. r.	ES	without atypia. Thinning of the aortic wall
Smith et al. 2000	28	10	L. internal carotid	Endoluminal stent graft; ligation	survived	alive (twins)	18	US	Neurofibroma
Roth et al. 2000	36	14	L. vertebral	Endovascular embolization	survived	alive	2	US	n. r.

APGAR: Appearance, Pulse, Grimace, Activity, Respiration; AVM: Arteriovenous Malformation; CS: Cesarean Section; ES: Spain; GA: Gestational Age; IUFT: Intrauterine Fetal Death; JP: Japan; L: Left; pp: Days Post-Partum; MY: Malaysia; NR: Not Reported; R: Right; UK: United Kingdom; US: United State of America.

Overall, 61 reports (39%) included a description of the histopathological findings. Elastin fragmentation and changes of the vessel wall structures were common features; likewise, neurofibroma or positive results for S-100 protein, a Schwann cell marker, was reported. In our case the wall of the ruptured iliac artery exhibits a thickened media with disrupted elastic fibers and increased smooth muscle cells in a disorderly arrangement. The intima of the iliac artery is not reliably depictable, the adventitia shows a discrete fibrosis. There is no evidence of interposed neurofibroma [17-19].

Discussion

Vessel ruptures in patients with NF1 are rare, illustrated by the fact that only case reports have been published. The mortality rate of 21.6% may be an underestimation. Most severe cases may go undiagnosed since they do not reach hospital in time for treatment. This assumption is supported by our own case, who went into hemorrhagic shock with cardiorespiratory arrest within two minutes after onset of symptoms; survival, and even survival without neurologic sequelae after 32 minutes to the return of spontaneous circulation was owed to the fact that the rupture occurred within the theatre premises of a large level I referral center, with immediate availability of specialists in vascular surgery and anesthesia, and blood products [20-23].

With 7.1% of reported cases covering pregnancy and the postpartum period, and the majority of published cases in the non-pregnant population reporting on women, female sex and the reproductive phase in particular, are overrepresented.

An adverse association between pregnancy and NF1 has been previously reported. The increase in number of café-au-lait spots and accelerated growth of neurofibromas has been attributed to the hormonal changes of pregnancy, especially to the rise in steroid hormone concentrations [24]. The hyperdynamic cardiovascular state of pregnancy, consisting of an increase in blood volume and cardiac output of some 40% may additionally contribute to the rupture of an affected vessel wall. No difference was present in the location of vessel rupture between pregnant and non-pregnant cases.

Results of our investigation are characterized by several limitations. These comprise the type of included publications. The risk of bias is particularly high for case reports. However, these were the only publications available. Furthermore, survival rates may be overestimated since non-successful cases may not be reported; additionally, cases may go undiagnosed if they do not reach hospital in time and postmortem diagnosis is not performed. Publication bias may also explain the high number of reports during pregnancy and postpartum. However, since women with NF1 tend to have a lower than average pregnancy rate, the risk of arterial rupture during pregnancy may even be higher.

Conclusion

In conclusion, vessel rupture is a rare but devastating complication of patients with NF1. Until now, screening and preventive measures are not available. A high level of suspicion, an immediate attention of a multidisciplinary team of (vascular) surgeons, anesthetists, radiologists, and in case of pregnancy. Obstetricians, with availability of large amounts of blood products are a prerequisite of successful treatment.

Competing interests

All authors declare that they have no competing interests.

No Funding.

Authors contributions

RP: literature review; Data analysis; Manuscript writing. SLS and GK: histological examination; Manuscript writing. AK and FV: surgical management; UG: prenatal management, manuscript writing. WMM: Data analysis; Patient management coordination; Manuscript writing. All authors read and approved the final manuscript.

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