Acta Anaesth. Bel., 2024, 75 | Suppl. 1: 115-123

Masterthesis / Review

Anesthetic considerations for the parturient with neurofibromatosis type 1

N. Govaerts[1], E. Roofthooft[2], M. Van de Velde[3]

[1]*Department of Anesthesiology, University Hospitals of Leuven, Leuven, Belgium;* [2]*GZA Hospitals, Antwerp, Belgium;* [3]*Department of Anesthesiology, University Hospitals of Leuven, Leuven, Belgium.*

Corresponding author: N. Govaerts, Herestraat 49, 3000 Leuven, Belgium. Email: nina.govaerts@gmail.com

Abstract

Neurofibromatosis type 1 (NF1) is a relative common genetic disorder affecting multiple major organ systems throughout the body like the central nervous system, cardiovascular system and respiratory system. As life expectancy extends beyond the childbearing years, an anaesthetist may come into contact with a pregnant woman with neurofibromatosis. The aim of this narrative review is to examine the current literature on how to safely anaesthetise the parturient with NF1 and highlight any difficulties that may be encountered. We reviewed two major databases up to May 2023. We conclude that patients with NF1 require a thorough preoperative assessment early in pregnancy, with particular attention to airway management, causes of hypertension and the presence of neuraxial disease involvement. An individual plan for anaesthesia needs to be made based on personal history and symptoms. Currently there is insufficient evidence to provide clear guidelines on the safe use of neuraxial anaesthesia in the NF1 population.

Keywords: **Anesthesia, Pregnancy, Neurofibromatosis 1.**

Introduction

Neurofibromatosis type 1 (NF1), often referred to as von Recklinghausen disease, is a common genetic disorder. It is inherited in an autosomal dominant manner, although 50% of the cases are caused by a de novo mutation. The affected gene lies on chromosome 17 and encodes for a protein called neurofibromin. Neurofibromin plays a role in tumour suppression. A defect in the gene therefore causes uncontrolled cell proliferation throughout the body. It is characterized by the growth of benign tumours, also known as neurofibromas[1-3].

NF1 has an incidence of 1 in 3500 people and has a penetration of 100%[4]. Clinical expression varies between patients and changes with age. One of the hallmarks for NF1 are the presence of multiple cafe-au-lait spots, which increase in size and number with time. The diagnostic criteria are shown in Table I[1-3].

Life-expectancy in the NF1 population is on average 8 years younger then in the general population[5]. Since NF1 does not affect fertility and the life expectancy exceeds the reproductive years, it is logical to assume that women with NF1 will become pregnant. Anesthetists need to be aware of the multisystemic complications associated with NF1 when evaluating a pregnant woman with a history of NF1. The aim of this review article is to report and discuss the known clinical important complications associated with NF1 during pregnancy.

Methods

We searched the Pubmed and Embase databases for literature using the search terms ‘anesthesia’ and ‘neurofibromatosis type 1’. An additional search was done with the search terms ‘neurofibromatosis type 1’ and ‘pregnancy complications’. Only articles written in English were included. The literature was searched until May 2023. We also screened the reference lists of the included articles. A PRISMA-flowchart[6] of the search strategy is shown in Figure 1.

Clinical effects of NF1 outside pregnancy

NF1 is a genetic disease that can affect mesodermal and ectodermal tissue, therefore it can cause various symptoms in multiple organ systems. It is important to note that expression might vary between patients[1-3]. Table II shows the most

Table I. — National institutes of Health criteria NF-1.

Patients should express two or more of the following clinical features
● At least six café-au-lait spots ● Prepubertal: >0.5cm ● Postpubertal: >1.0 cm ● Axillary or inguinal freckling ● Two or more neurofibromas of any type or one or more plexiform neurofibroma ● Two or more iris hamartomas (Lisch nodules) ● Optic glioma ● A distinctive bony lesion ● Sphenoid wing dysplasia ● Long-bone dysplasia or thinning of long-bone cortex ● First-degree family member with NF-1

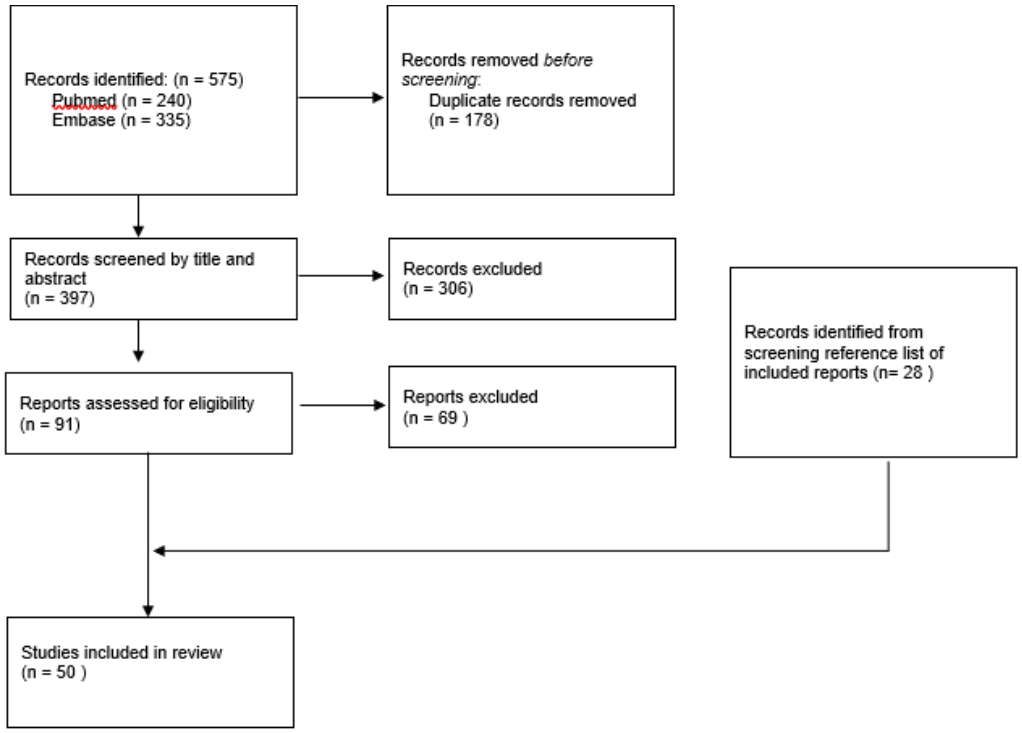

Fig. 1 — PRISMA[6] flow chart.

common symptoms or pathologies associated with NF1.

NF1 is known to form neurofibromas. Neurofibromas are benign tumours of nerves or nerve roots. They consist of Schwann cells, perineural cells, fibroblasts or mastcells[1,2]. They are benign but can grow along the nerve or grow locally, causing symptoms due to compression. Neurofibromas can be classified in three categories: cutaneous, subcutaneous and plexiform neurofibromas. Most of the neurofibromas, except cutaneous, are not visible on clinical examination since they lie in deeper tissue layers. Both subcutaneous and plexiform neurofibromas can progress over time to malignant peripheral nerve sheath tumours[1-3]. The NF1 population has a 2.5 to 4-fold increased risk of developing brain and connective tissue tumours then the non-affected population. The population also has a high incidence of other tumours such as gastrointestinal stromal tumours (GISTs), pheochromocytomas, breast cancer and leukaemia[1,2,7].

There is also an increased cardiovascular risk in patients with NF1 since they have a higher incidence of hypertension and vasculopathies of the small, medium and large vessels. Vasculopathies might vary from the formation of aneurysms to stenosis[7]. The pathogenesis is not fully understood, but the NF1 gene might affect the vascular endothelial cells and smooth muscle cells, resulting in increased growth and proliferation[8]. Also increased levels of inflammatory cells and cytokines are present in the blood of patients with NF1, resulting in development of atherosclerosis[8].

Pregnancy and NF1

Given that NF1 affects multiple organ systems, it is reasonable to assume that it may impact pregnancy. Case series report complications during

Table II. — Clinical expression of NF1.

Symptoms more common in NF1 population
Cutaneous findings: ● Café-au-lait spots ● Freckling of axillary or inguinal region
Ophthalmologic finding: ● Iris hamartomas ● Optic gliomas
Tumours: ● Neurofibromas: cutaneous, subcutaneous and plexiform ● Malignant nerve sheath tumours ● CNS tumours: ● Optic gliomas ● Astrocytomas ● Gliomas: brainstem or cerebellar ● Non-CNS tumours: higher incidence then normal population ● Rhabdomyosarcomas ● Carcinoid tumours ● Myeloid leukaemia ● Gastrointestinal stromal tumours (GISTs) ● Breast cancer ● Pheochromocytoma
Skeletal deformities: ● Scoliosis ● Pseudoarthrosis ● Short stature ● Osteopenia ● Sphenoid wing dysplasia
Cardiovascular abnormalities: ● Vascular stenosis ● Pulmonary artery ● Renal artery ● Carotid artery ● Coarctatio aortae ● Aneurysms ● Hypertension
Neurologic abnormalities: ● Learning difficulties ● Attnetion deficit hyperactivity disorder (ADHD) ● Seizures ● Macrocephalie ● Perihepal neuropathy ● Aqua ductal stenosis

pregnancy such as complicated delivery due to pelvic neurofibromas[3], vascular complications like rupture of aneurysms[9,10] pheochromocytoma[11] and transformation and proliferation of known tumours[12,13].

A large Danish population-based cohort study investigated pregnancy outcomes in women with NF1[14]. They concluded that there was a similar risk for pregnancy between women with NF1 and the control population after correcting for potential medical consequences of NF1, but that women with NF1 were more likely to have spontaneous abortions and stillbirths[14].

Terry et al. performed a population-based retrospective cohort study in the US between 1988-2009, to determine if vascular and other complications are more frequent during pregnancy of women with NF1. They investigated outcomes such as the prevalence of pre-eclampsia, intrauterine-growth-restriction (IUGR), stillbirth, cardiovascular anomalies, deep venous thrombosis, pulmonary embolism, acute cardiac complications, preterm labor, the need for a caesarean section (CS) and mortality. Patients with NF1 had significant more pre-eclampsia, IUGR, CS, gestational hypertension, preterm labor and cerebrovascular disease. They concluded that there was an increased maternal morbidity, but no increased risk of mortality[15].

Another retrospective Finnish cohort study included 1410 patients with NF1 between 1987 and 2013. Each NF1 patient was matched with

ten non-NF1 patients in the control group. After exclusion of men and non-pregnant women, 176 pregnant NF1 patients remained in the study group. They accounted for 375 deliveries. They concluded that IUGR, oligohydramnios, placental abruption, hypertension and preeclampsia were more frequent in the NF1 population[16].

Case reports mention growth of cutaneous and subcutaneous neurofibromas during pregnancy[17]. One case report mentions a postpartum paraparesis due to rapid growth of an extradural neurofibroma, with compression of the conus medullaris[18]. Spontaneous regression after pregnancy is also documented[19,20]. There are authors who believe that neurofibromas grow, in size and number under influence of the hormonal changes during pregnancy[21-23]. In vitro studies showed that some neurofibromas express progesterone receptors[21-23] and that the exposure of neurofibromas to progesterone or estrogen has an effect on proliferation and apoptosis[22].

Lennert Well et al. investigated the effect of pregnancy on the growth-dynamics of cutaneous and plexiform neurofibromas by MRI imaging before and after pregnancy. They compared 13 mothers with NF1 to 13 age-matched nullipara, nulli gravida NF1 patients. Plexiform neurofibromas were detected in 46% of the women. Follow-up showed no new development of plexiform neurofibromas, nor a significant difference in growth rate. The cutaneous neurofibromas grew in both groups, but there was no significant difference in increase between the study groups. They concluded that neurofibromas grow with time, but pregnancy does not change the growth rate[21].

The American College of Medical Genetics and Genomics (ACMG) recommendations state that referral of a parturient to a high-risk obstetric practice should be considered due to the high morbidity and complex pathology[7].

Anaesthetic considerations for the pregnant patient with NF1

Respiratory system

Planned and unplanned CS is frequent during pregnancy and labor and delivery. Although neuraxial anaesthesia is preferred, frequently general anaesthesia might be required. Airway management for the pregnant population is known to be challenging due to the physiologic changes associated with pregnancy and an anaesthetist needs to be prepared for difficult airway management24,25.

Neurofibromatosis can cause upper airway obstruction during anaesthetic induction due to macroglossia and the presence of plexiform fibromas in the pharynx, larynx, and supraglottic region, making endotracheal intubation even more challenging[3,26-28]. Tracheal and bronchial compression by mediastinal neurofibroma have been reported with known respiratory symptoms and challenging airway management[29,30]. Also rupture of arteriovenous malformations in the neck region with secondary compression on the larynx and trachea are reported[31,32]. Therefore, an anaesthetist needs to be extra cautious during the preoperative evaluation for signs that are suspect for difficult intubation. Clinical symptoms like difficulties with swallowing, deviated trachea or hoarse voice need extra investigation by indirect laryngoscopy, CT or MRI[3].

Whether neurofibromatosis is associated with higher risk of pulmonary fibrosis remains controversial. However, some reports suggested that pulmonary fibrosis starts at adult age and is progressive, which may lead to pulmonary hypertension and right ventricular failure[3].

Ten percent of the patients with NF1 have a deviation of the thoracic spinal curvature, some of them might have a reduction in lung volume, leading to restrictive lung disease[3].

When assessing a patient preoperatively, an anaesthetist must spend additional time evaluating the airway and chest wall. Furthermore, additional examinations, such as X-rays and lung volume measurements, may be necessary[1,3].

Cardiovascular

Patients with NF1 have higher cardiovascular comorbidities than the general population. The comorbidities include multiple vasculopathies, arterial hypertension and vena cava obstruction[3].

Preoperative evaluation should include reviewing cardiovascular history including echocardiography if available, screening for hypertension and maintaining alert for the possibility of pheochromocytoma[1].

Analysis of longitudinal NRS data

Arterial hypertension affects 6% of the NF1 population. In most cases, patients have essential hypertension. However, in 30% of cases, it is secondary to aortic coarctation, renal artery stenosis, or a pheochromocytoma[3].

Multiple retrospective studies concluded that NF1 patients have a higher rate of cardiovascular complications during pregnancy[15,16].

Terry et al. showed that chronic hypertension and renal disease were more common in the NF1 group. They also reported that women with NF1 had higher odds to experience gestational hypertension, preeclampsia, cardiovascular

disease, preterm labor and IUGR. IUGR is likely due to vasculopathies of the placental vascular bed, which can result in suboptimal bloodflow to the foetus[1].

Since 0.01-5.7% of the population with NF1 might present with pheochromocytoma[33], an anaesthetist always needs to be aware of the possibility that therapy resistant hypertension may be a symptom of undiagnosed pheochromocytoma.

Multiple case reports show different outcomes for pregnant patients with NF1 and pheochromocytoma[11,34,35].

Pheochromocytoma during pregnancy is an extremely rare condition, estimated to occur in only 0.007% of pregnancies. It is misdiagnosed in 20% of cases, as other causes of hypertension during pregnancy are more prevalent[36]. This misdiagnosis might have serious consequences, because adequate treatment reduces maternal mortality from 40-60% to less than 5% and foetal mortality 60% to less than 15%[37].

According to Lenders et al. differentiating gestational hypertension and hypertension secondary to pheochromocytoma can be made on clinical grounds. Alarm symptoms include early onset hypertension before 20 weeks of gestation, orthostatic hypotension and paroxysmal symptoms (such as tachycardia, pallor, palpitations and headaches)[37]. Therefore, ACMG recommends considering the possibility of a pheochromocytoma in NF1 patients who are older than 30 years, are pregnant and/or have paroxysmal hypertension, hypertension associated headaches or palpitations. Biochemical screening is only necessary if the patient is symptomatic. Plasma free metanephrine concentration testing is the most sensitive. A 24-hour urine collection for catecholamine concentration should only be performed when the plasma free metanephrine concentration is elevated, but lower than fourfold the baseline[7]. Signs more specific for gestational hypertension include oedema, proteinuria and haemolysis, elevated liver enzymes, and low platelet count syndrome (HELLP)[37].

The only definitive treatment for a pheochromocytoma is resection of the adrenal gland. During pregnancy, it is preferred to use a laparoscopic transperitoneal approach while in lateral decubitus position. If the tumour is located on the left side, positioning the patient on the right side is challenging because it increases the risk of haemodynamic instability and placental hypoperfusion. Timing of surgery remains a matter of debate. However, it is generally agreed that surgery should be performed before 24 weeks of gestation. In the second trimester, the risks to the foetus are minimal, and the anatomical approach is the simplest. If diagnosed after 24 weeks, it is recommended to begin medical therapy and delay the removal until after delivery[37,38].

Medical therapy aims to reduce the risk of complications due to massive release of catecholamines. Alpha-adrenoceptor blockade is a hallmark. The most used products are phenoxybenzamine and doxazosin. While phenoxybenzamine is a noncompetitive alpha 1 and 2 antagonist and doxazosin is a competitive selective alpha 1 antagonist, the latter is preferred because it has less foetal effects. Doxazosin dosing starts at 2 mg each day and may be increased to 16 to 32 mg a day. Secondary after a few days of alpha adrenoceptor blockage the association of a beta blockade may be necessary to prevent and treat tachyarrhythmias[37,39].

The use of calcium channel blockers and labetalol as monotherapy for presurgical management of pheochromocytoma during pregnancy remains controversial. When using a beta antagonist Gruber et al. recommends using a selective beta-1 receptor blocker, since beta-2 antagonism may reduce myometrium relaxation[39]. Labetalol in monotherapy has more beta-effect than alpha blocking efficacy and has been associated with reports of hypertensive crises. Therefore, it is not recommended to use labetalol in monotherapy[37,39]. Acute catecholamine crisis needs to be treated with short acting calcium channel blockers like nicardipine. Association of magnesium sulphate may cause additional vasodilation, may reduce catecholamine release, and reduce sensitivity for the alpha adrenoreceptor. Tachyarrhythmias should be treated with short acting beta blockade such as esmolol[37,38].

Lenders et al. acknowledge the lack of clear guidelines which target blood pressure should be used in these cases. They advise to use the same target tensions that are used for treatment of gestational hypertension 140/90mmHg[37].

Vasculopathies

NF1 is associated with vasculopathies which include arterial stenosis, AV malformations, aneurysms and vessel compression or invasion by a neurofibroma[40]. Most often it is arterial involvement, but venous and pulmonary vessel involvement also occurs[41]. The incidence of vasculopathies in NF1 population is estimated to be 0.4-6.4%[42-44].

Frequently vasculopathies remain asymptomatic[40]. However, due to cardiovascular changes in pregnancy due to the increased blood volume and hormonal effects on vessel walls, they can become symptomatic and can cause major haemorrhage[9,10,31].

The ACMG recommends that when a patient is under 30 years old, pregnant and/or with clinical examination a doctor hears abdominal bruits, investigations for renal artery stenosis or aneurysm need to be made[7].

Neuraxial anesthesia

NF1 is associated with the presence of meningiomas, hydrocephalus and gliomas[27].

The risk of developing any type of brain tumour is at least five times higher in the NF1 population. Fifteen to twenty per cent of patients with NF1 have low-grade glial neoplasms, the most common of which is optic glioma, but cerebellar, cortical and brainstem involvement can also occur. Optic gliomas typically occur in young children, whereas brainstem involvement occurs later in adolescence. Patients with brainstem involvement present with symptoms such as headache, lethargy, cranial neuropathy, and gait instability[2]. Involvement of the brainstem might also result in central hypoventilation syndromes, which might cause difficulties with weaning after invasive ventilation[1,3].

Patients who have intracranial tumours are at risk of elevated intracranial pressure. Schmidt et al reported a case where a NF1 parturient who lived with a stable pilocytic astrocytoma for 20 years suddenly died at 24 weeks gestations because of transformation of the astrocytoma in to a haemorrhagic high grade glioma, causing elevated intracranial pressure and cerebellar tonsil herniation. They concluded their report by recommending carefully monitoring all known glial tumours during pregnancy[12].

Anaesthetists must be aware of the possibility of an undiagnosed intracranial tumour when evaluating a patient preoperatively. Symptoms suspect of elevated intracranial pressure should be investigated.

NF1 can also lead to various musculoskeletal complications such as pseudoarthrosis, bone lesions, scoliosis, kyphoscoliosis, and osteoporosis. It is also associated with spina bifida and spinal tumours[27]. Spinal tumours have been reported in 40% of the NF1 population, some being asymptomatic. They usually are located laterally from the intervertebral foramen, which make them prone to puncture during epidural analgesia[45]. Neurofibroma might be highly vascularized and can therefore cause epidural hematoma when punctured. Tumour spread might theoretically also occur when puncturing a neurofibroma[12]. In addition, due to scoliosis it might also be technically more difficult to perform an epidural or spinal anesthesia[1,3].

All of the above-mentioned reasons might be relative contraindications for neuraxial anesthesia in the NF1 population[3,46]. However there are case series which report successful use of neuraxial anaesthesia in the NF1 population[47,48] and to our knowledge only one which reports epidural haematoma after puncture[49]. Galvan et al. reported the successful use of MRI imaging during labor to exclude neurofibroma and high intracranial pressure before deciding on which anaesthesia technique to use[50]. El Amri concluded in 2020 that spinal imaging is recommended[46].

The ACMG guidelines in 2018 however state that because they did not find sufficient evidence of significant adverse events or outcomes in women with NF1 undergoing epidural anesthesia, neuraxial imagining is probably not needed and neuraxial anesthesia techniques may be considered safe if needed[7].

Discussion

NF1 is a common genetic disease associated with various comorbidities. As the clinical manifestation varies between patients, an anaesthetist must prepare a treatment plan on an individual level. To our knowledge there are no guidelines on how to evaluate a pregnant patient with NF1 in the preoperative setting. In our opinion, a thorough preoperative assessment by an anaesthetist is essential to minimize the risks during labor. Ideally, patients should be assessed twice: early in pregnancy to plan additional investigations, and just before the expected date of delivery to see if any symptoms have changed to rule out disease progression.

Special attention is needed for symptoms that might predict difficult airway management like problems with swallowing, deviated trachea or hoarse voice. If severe scoliosis is present respiratory function tests might be useful. Screening for arterial hypertension is essential in cardiovascular evaluation. When a patient has an elevated blood pressure the anaesthesist must differentiate between gestational hypertension and other causes for hypertension like renal artery stenosis and pheochromocytoma. Evaluating the spine clinically for scoliosis or cutaneous neurofibroma is important. Reviewing patient history and previous scans might be helpful, but the practitioner also needs to be aware that new neurofibromas can occur during pregnancy. When the patient shows symptoms of new neurological involvement like pain, weakness or paresthesia or shows symptoms suggestive of high intracranial pressure extra investigations should be made

like CT of MRI scanning. Leffert et al. give clear guidelines on how to approach a patient with elevated intracranial pressure for neuraxial anesthesia[15].

The most common interaction between an anaesthesist and parturient is during labor. Historically the recommendation in most articles was not to perform neuraxial anaesthesia in a patient with NF1, because the risk of epidural hematoma was too high and because of the risk of elevated intracranial pressure. Elevated intracranial pressure is a contraindication for preforming neuraxial anaesthesia[51]. Since caesarean section is more common in the NF1 population[15,16] the only alternative for neuraxial anesthesia is general anesthesia. General anesthesia might carry a risk for mother and fetus because of the difficult airway management, hemodynamic changes and effect of anesthesia on the foetus. In addition it might also affect the mothers emotional experience of the birth of her child. Analgesia during labor becomes more standard care in developed countries. All of the above indicate the need for clear guidelines on the use of neuraxial anesthesia in the NF1 population. At this moment, we believe there is not enough high-quality research to make reliable recommendations. To our knowledge there is only one guideline that recommends to preform neuraxial anesthesia in the NF1 population without ruling out the presence of spinal neurofibromas. They made the recommendation based on the lack of complications mentioned after neuraxial anesthesia in the NF1 population[7].

The limited use of neuraxial anesthesia in this population16 however, may contribute in our opinion to the paucity of reports on complications after epidural of spinal anesthesia. Additionally, in vitro studies have shown that some neurofibromas have hormone-sensitive receptors[22,23], and case reports have mentioned the growth of neurofibromas during pregnancy[19,20]. So far there is only one study been conducted that systematically followed up the growth rate of neurofibroma in vivo and objectivated their size by use of MRI. Although Well et al. did not find a significant difference in growth rate of neurofibromas during pregnancy when compared to the general population. The study population was rather small and the timing after evaluating growth was late after delivery. So possible regression might have occurred[21].

Therefore in our opinion to ensure patient safety, MRI scanning might be indicated in patients known with spinal or paraspinal neurofibromas since growth of neurofibroma during pregnancy remains controversial. If patients experience symptoms which might indicate spinal or paraspinal neurofibromas or elevated intracranial pressure, extra investigations need to be made by imaging to rule out contraindications for neuraxial anesthesia.

Conclusion

Neurofibromatosis type 1 is a complex multi organ affecting disease. Patients with NF1 need special counseling during their pregnancy and preoperative evaluation is necessary. At this moment there is no hard evidence to support that neuraxial anesthesia is completely safe, although the reports on complications are minimal. Further investigations need to be made to make clear evidence based guidelines on whether neuraxial anesthesia should be preformed and if neuraxial imaging is necessary.

References

1. Fox CJ, Tomajian S, Kaye AJ, Russo S, Abadie JV, Kaye AD. Perioperative management of neurofibromatosis type 1. Ochsner J. 2012;12(2):111–21.
2. Hirbe AC, Gutmann DH. Neurofibromatosis type 1: a multidisciplinary approach to care. Lancet Neurol. 2014 Aug;13(8):834–43.
3. Hirsch NP, Murphy A, Radcliffe JJ. Neurofibromatosis: clinical presentations and anaesthetic implications. Br J Anaesth [Internet]. 2001 Apr;86(4):555–64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11573632
4. Friedman JM. Epidemiology of neurofibromatosis type 1. Am J Med Genet - Semin Med Genet. 1999;89(1):1–6.
5. Evans DGR, O'Hara C, Wilding A, Ingham SL, Howard E, Dawson J, et al. Mortality in neurofibromatosis 1: In North West England: An assessment of actuarial survival in a region of the UK since 1989. Eur J Hum Genet. 2011;19(11):1187–91.
6. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ [Internet]. 2021 Mar 29;372:n71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33782057
7. Stewart DR, Korf BR, Nathanson KL, Stevenson DA, Yohay K. Care of adults with neurofibromatosis type 1: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med [Internet]. 2018;20(7):671–82. Available from: https://doi.org/10.1038/gim.2018.28
8. Lasater EA, Li F, Bessler WK, Estes ML, Vemula S, Hingtgen CM, et al. Genetic and cellular evidence of vascular inflammation in neurofibromin-deficient mice and humans. J Clin Invest. 2010;120(3):859–70.
9. Tateishi A, Okada M, Nakai M, Yokota Y, Miyamoto Y. Spontaneous ascending aortic rupture in a pregnant woman with neurofibromatosis type 1. Gen Thorac Cardiovasc Surg. 2019 Nov 1;67(11):979–81.
10. Narasimman S, Govindasamy H, Seevalingam KK, Paramasvaran G, Ramasamy U. Spontaneous massive haemothorax in the peri-partum period of an undiagnosed neurofibromatosis type 1 patient - A surgical perspective. Med J Malaysia [Internet]. 2019 Feb;74(1):99–101. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30846675
11. Cecchi R, Frati P, Capri O, Cipolloni L. A Rare Case of Sudden Death Due to Hypotension during Cesarean Section in a Woman Suffering from Pheochromocytoma and Neurofibromatosis. J Forensic Sci. 2013;58(6):1636–9.

12. Schmidt BT, Hanna A. Deadly Proliferation and Transformation of Pilocytic Astrocytoma in Pregnancy. World Neurosurg [Internet]. 2020 Jan;133:99–103. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1878875019325677
13. Ramos-Zúñiga R, Saldaña-Koppel DA. Neurofibromatosis type 1 and pregnancy: The transformation of a nodular to cystic neurofibroma in the cervical region. Vol. 6, Surgical neurology international. United States; 2015. p. S487-9.
14. Kenborg L, Boschini C, Bidstrup PE, Dalton SO, Doser K, Nielsen TT, et al. Pregnancy outcomes in women with neurofibromatosis 1: A Danish population-based cohort study. J Med Genet. 2021;
15. Terry AR, Barker FG, Leffert L, Bateman BT, Souter I, Plotkin SR. Neurofibromatosis type 1 and pregnancy complications: A population-based study. Am J Obstet Gynecol. 2013;209(1):46.e1-46.e8.
16. Leppävirta J, Kallionpää RA, Uusitalo E, Vahlberg T, Pöyhönen M, Timonen S, et al. The pregnancy in neurofibromatosis 1: A retrospective register-based total population study. Am J Med Genet Part A. 2017 Oct 1;173(10):2641–8.
17. Yahya H, Sani H. Eruptive neurofibromas in pregnancy. Ann Afr Med. 2020;19(2):150–2.
18. Dham BS, Kwa DM, Campellone J V. Postpartum paraparesis from spinal neurofibroma. Spine J [Internet]. 2012 Jul;12(7):e5–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1529943012004482
19. Dugoff L, Sujansky E. Neurof ibromatosis Type 1 and Pregnancy. Vol. 66, American Journal of Medical Genetics. 1996.
20. Posma E, Aalbers R, Kurniawan YS, Essen AJ, Peeters PMJG, Loon AJ. Neurofibromatosis type I and pregnancy: a fatal attraction?. Development of malignant schwannoma during pregnancy in a patient with neurofibromatosis type I. BJOG An Int J Obstet Gynaecol. 2003;110(5):530–2.
21. Well L, Jaeger A, Kehrer-Sawatzki H, Farschtschi S, Avanesov M, Sauer M, et al. The effect of pregnancy on growth-dynamics of neurofibromas in Neurofibromatosis type 1. Spradley FT, editor. PLoS One [Internet]. 2020 Apr 28;15(4):e0232031. Available from: https://dx.plos.org/10.1371/journal.pone.0232031
22. Fishbein L, Zhang X, Fisher LB, Li H, Campbell-Thompson M, Yachnis A, et al. In vitro studies of steroid hormones in neurofibromatosis 1 tumors and schwann cells. Mol Carcinog [Internet]. 2007 Jul 28;46(7):512–23. Available from: https://onlinelibrary.wiley.com/doi/10.1002/mc.20236
23. Roth TM, Petty EM, Barald KF. The role of steroid hormones in the NF1 phenotype: Focus on pregnancy. Am J Med Genet Part A. 2008;146(12):1624–33.
24. Mushambi MC, Athanassoglou V, Kinsella SM. Anticipated difficult airway during obstetric general anaesthesia: narrative literature review and management recommendations. Anaesthesia [Internet]. 2020 Jul 6;75(7):945–61. Available from: https://associationofanaesthetists-publications.onlinelibrary.wiley.com/doi/10.1111/anae.15007
25. Mushambi MC, Kinsella SM, Popat M, Swales H, Ramaswamy KK, Winton AL, et al. Obstetric Anaesthetists' Association and Difficult Airway Society guidelines for the management of difficult and failed tracheal intubation in obstetrics. Anaesthesia [Internet]. 2015 Nov 8;70(11):1286–306. Available from: https://associationofanaesthetists-publications.onlinelibrary.wiley.com/doi/10.1111/anae.13260
26. Lee WY, Shin YS, Lim CS, Chung WS, Kim BM. Spinal anesthesia for emergency cesarean section in a preeclampsia patient diagnosed with type 1 neurofibromatosis. Korean J Anesthesiol. 2014;65(6 SUPPL.):91–2.
27. Mcdonald JS, D M. CASE REPORT : Anesthetic Consideratons in von Recklinghausen ' s Disease. 1980;(April):1980.
28. CROZIER WC. Upper airway obstruction in neurofibromatosis. Anaesthesia. 1987;42(11):1209–11.
29. Dodge TL, Mahaffey JE, Thomas JD. The anesthetic management of a patient with an obstructing intratracheal mass: A case report. Anesth Analg. 1977;56(2):295–8.
30. El Oakley R, Grotte GJ. Progressive tracheal and superior vena caval compression caused by benign neurofibromatosis. Thorax. 1994;49(4):381.
31. Davidson A, Beddoes P, Patel J, Hunningher A. Rapid upper airway obstruction after arteriovenous malformation rupture in a patient with neurofibromatosis. Anaesth Reports. 2021;9(2):1–4.
32. Souldi H, Bajja MY, Chenguir M, Abada R, Rouadi S, Roubal M, et al. Ruptured left external carotid artery aneurysm presenting as upper airway obstruction in von Recklinghausen's disease. Int J Surg Case Rep [Internet]. 2016;26:170–2. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2210261216302462
33. Walther MM, Herring J, Enquist E, Keiser HR, Linehan WM. VON RECKLINGHAUSEN′S DISEASE AND PHEOCHROMOCYTOMAS. J Urol [Internet]. 1999 Nov;162(5):1582–6. Available from: http://www.jurology.com/doi/10.1016/S0022-5347%2805%2968171-2
34. Remón-Ruiz P, Aliaga-Verdugo A, Guerrero-Vázquez R. Pheochromocytoma in neurofibromatosis type 1 during pregnancy. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 2017 Feb;33(2):93–5.
35. Takahashi N, Nishijima K, Orisaka M, Tsuyoshi H, Kurokawa T, Kato K, et al. Amniotic Fluid Embolism Triggered By Hypertensive Crisis Due to Undiagnosed Pheochromocytoma in a Pregnant Subject With Neurofibromatosis Type 1. AACE Clin Case Reports [Internet]. 2015;1(3):e178–81. Available from: https://doi.org/10.4158/EP14108.CR
36. Ahlawat SK, Jain S, Kumari S, Varma S, Sharma BK. Pheochromocytoma Associated With Pregnancy: Case Report and Review of the Literature. Obstet Gynecol Surv [Internet]. 1999 Nov;54(11):728. Available from: http://journals.lww.com/00006254-199911000-00025
37. Lenders JWM, Langton K, Langenhuijsen JF, Eisenhofer G. Pheochromocytoma and Pregnancy. Endocrinol Metab Clin North Am [Internet]. 2019 Sep;48(3):605–17. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0889852919300350
38. Bartz-Kurycki MA, Dream S, Wang TS. Surgical treatment of adrenal tumors during pregnancy. Rev Endocr Metab Disord [Internet]. 2023 Feb;24(1):107–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/35776233
39. Gruber LM, Young WF, Bancos I. Pheochromocytoma and Paraganglioma in Pregnancy: a New Era. Curr Cardiol Rep. 2021;23(6):1–8.
40. Oderich GS, Sullivan TM, Bower TC, Gloviczki P, Miller D V., Babovic-Vuksanovic D, et al. Vascular abnormalities in patients with neurofibromatosis syndrome type I: Clinical spectrum, management, and results. J Vasc Surg [Internet]. 2007 Sep;46(3):475-484.e1. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0741521407007227
41. Stewart DR, Cogan JD, Kramer MR, Miller WT, Christiansen LE, Pauciulo MW, et al. Is pulmonary arterial hypertension in neurofibromatosis type 1 secondary to a plexogenic arteriopathy? Chest [Internet]. 2007 Sep;132(3):798–808. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17573495
42. Lin AE, Birch PH, Korf BR, Tenconi R, Niimura M, Poyhonen M, et al. Cardiovascular malformations and other cardiovascular abnormalities in neurofibromatosis 1. Am J Med Genet [Internet]. 2000 Nov 13;95(2):108–17. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11078559

43.Hamilton SJ, Friedman JM. Insights into the pathogenesis of neurofibromatosis 1 vasculopathy. Clin Genet [Internet]. 2000 Nov;58(5):341–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11140831
44.Friedman JM, Arbiser J, Epstein JA, Gutmann DH, Huot SJ, Lin AE, et al. Cardiovascular disease in neurofibromatosis 1: report of the NF1 Cardiovascular Task Force. Genet Med [Internet]. 2002;4(3):105–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12180143
45.Thakkar SD, Feigen U, Mautner VF. Spinal tumours in neurofibromatosis type 1: An MRI study of frequency, multiplicity and variety. Neuroradiology. 1999;41(9):625–9.
46.EL AMRI A, EL ABDI F, ELHASNAOUI MA, EL KOUNDI A. Neurofibromatosis during pregnancy, what about anesthesia? Anaesthesia, Pain Intensive Care. 2020 Dec 4;24(6).
47.Dounas M, Mercier FJ, Lhuissier C, Benhamou D, Crochetière C, Muir H. Epidural analgesia for labour in a parturient with neurofibromatosis. Can J Anaesth. 1995;42(5):420–4.
48.Singh T, Hooda S, Anand A, Kaur K, Bala R. Anesthetic consideration in a preeclamptic parturient with Von Recklinghausen′s neurofibromatosis. J Obstet Anaesth Crit Care. 2014;4(1):38.
49.Esler MD, Durbridge J, Kirby S. Epidural haematoma after dural puncture in a parturient with neurofibromatosis. Br J Anaesth [Internet]. 2001;87(6):932–4. Available from: http://dx.doi.org/10.1093/bja/87.6.932
50.Galvan JM, Hofkamp MP. Usefulness of intrapartum magnetic resonance imaging for a parturient with neurofibromatosis type 1 during induction of labor for preeclampsia. Baylor Univ Med Cent Proc. 2018;31(1):92–3.
51.Leffert LR, Schwamm LH. Neuraxial anesthesia in parturients with intracranial pathology: A comprehensive review and reassessment of risk. Anesthesiology. 2013;119(3):703–18.

doi.org/10.56126/76.S1.07