The Ochsner Journal 12:111–121, 2012

Perioperative Management of Neurofibromatosis Type 1

Charles J. Fox, MD,* Samir Tomajian, MD,* Aaron J. Kaye,†‡ Stephanie Russo,* Jacqueline Volpi Abadie, MD,†¶ Alan D. Kaye, PhD, MD§

**Department of Anesthesiology, Tulane University Medical Center, New Orleans, LA*
†Department of Anesthesiology, Louisiana State University School of Medicine, New Orleans, LA
‡Stanford University, Palo Alto, CA
§Departments of Anesthesiology and Pharmacology, Louisiana State University Health Sciences Center, New Orleans, LA

ABSTRACT

Neurofibromatosis type 1 (neurofibromatosis-1), a relatively common single-gene disorder, is caused by a mutation of the NF1 gene that results in a loss of activity or in a nonfunctional neurofibromin protein. Clinical anesthesiologists may find patients with neurofibromatosis-1 challenging because this condition may affect most organ systems and result in a wide variety of presentations and clinical implications. Current neurofibromatosis-1 research studies include genotype-phenotype correlations, investigation of the pathoetiology behind the different clinical manifestations of neurofibromatosis-1, and the search for treatment options for the different features of the disorder. Neurofibromatosis-1–associated complications of the central nervous, respiratory, cardiovascular, musculoskeletal, and gastrointestinal and genitourinary systems all present various degrees of considerations for anesthesiologists. Additionally, neurofibromatosis-1 has dramatic implications for pregnant women.

INTRODUCTION

Neurofibromatosis type 1 is an autosomal dominant neurocutaneous disorder. It is one of the most common inherited single-gene disorders, with an incidence of 1 in 3,500 individuals at birth and affecting approximately 75,000 people in the United States.[1,2] Initially described in 1882 by Dr Friedrich Daniel von Recklinghausen and accordingly called von Recklinghausen disease,[1] neurofibromatosis-1 impacts individuals across all ethnic groups and displays diverse manifestations that can affect multiple organ systems.[2] Neurofibromatosis-1 exhibits complete penetrance, meaning that 100% of patients with the disorder have some phenotypic expression during their lifetimes. Neurofibromatosis-1 also demonstrates variable expressivity, meaning that the severity of the condition and the clinical manifestations vary across individuals with the same genotype.[3] Consequently, the clinical manifestations are extremely variable and unpredictable among individuals with this disease, even among individuals with the same genotype. This review addresses the pathogenesis, diagnosis, clinical manifestations, anesthetic implications, and management of neurofibromatosis-1. Anesthesiologists must be aware of and consider each of the multisystemic complications of the disorder when evaluating and managing patients for surgical procedures.

Address correspondence to
Charles J. Fox, MD
Department of Anesthesiology
Tulane University Medical Center
1430 Tulane Ave.
New Orleans, LA 70112
Tel: (504) 988-5068
Fax: (504) 988-1743
Email: charles.fox@hcahealthcare.com

Keywords: Anesthesia, café-au-lait macules, NF1 gene, neurofibromatosis type 1

The authors have no financial or proprietary interest in the subject matter of this article.

¶Dr Abadie is now with the Department of Anesthesiology, Ochsner Clinic Foundation, New Orleans, LA.

PATHOGENESIS

Neurofibromatosis-1 is caused by a heterozygous mutation in the NF1 gene, which codes for the protein neurofibromin and results in a loss of functional protein. Originally identified by Cawthon et al[4] and Wallace et al[5] in 1990, the large NF1 gene is located on chromosome 17q11.2. This gene comprises 60 exons and spans 350 kb of genomic DNA.[6,7] The protein product of this gene, neurofibromin, is made up of 2,818 amino acids and is present in various tissue types although concentrated in nervous tissue.[6,8] The NF1 gene regulates the expression or deregulation of the protein neurofibromin. Neurofibromin's function is not completely understood, but it is known to be a guanosine triphosphatase–activating protein that functions to downregulate p21-ras (rat sarcoma), a cellular protooncogene that

is an important regulator of cell growth. Therefore, neurofibromin plays a role in the control of cell division[9] and possesses certain tumor suppression qualities.[1,10]

Many types of mutations can result in neurofibromatosis-1, including insertions, deletions, base substitutions, chromosomal rearrangements, translocations, splice mutations, alterations of the 3′ untranslated region, and most frequently nonsense or frameshift mutations.[6,11,12] These mutations can occur in the germline or in the somatic cells of an individual.[13] The NF1 gene has one of the highest mutation rates of any gene within the human genome, recorded at approximately 1 per 10,000 alleles per generation.[1] More than 500 different mutations in the NF1 gene have been identified. Familial mutations cause approximately half of all neurofibromatosis-1 cases, and the other half stem from new, spontaneous mutations.[1]

Because of the possibility of new mutations, neurofibromatosis can be demonstrated in families with no history of the disease. No difference in the severity of the disease can be found in patients with familial mutations versus those with new mutations.[11] In a study of NF1 gene mutations, Ars et al[14] found that 85 of 189 unrelated patients (45%) with NF1 mutations have recurrent mutations. This study proved that similar mutations of the NF1 gene spontaneously occur in unrelated patients. Interestingly, sporadic germline mutations tend to occur in the paternally derived chromosome.[13,15] Classifying these different mutations may provide the source for the variable symptoms associated with neurofibromatosis and enhance genetic testing for this disease.

The mutation of the NF1 gene results in either a loss of function or a nonfunctional neurofibromin protein that allows for Ras activation and ultimately for uncontrolled cell proliferation.[12] The deficiency of neurofibromin affects cell types throughout the entire body, especially the neural crest cells that include Schwann cells, melanocytes, and endoneurial fibroblasts. Additionally, heterozygosity can be lost—a second-hit mutation to the normal NF1 allele—resulting in 2 abnormal NF1 genes.[10] According to several studies, this process seems to be the mechanism behind the formation of neurofibromas and café-au-lait macules (CALMs).[13] However, this mutation is not the cause of all of the features of this disease; current studies are still trying to elucidate the exact mechanisms. The actual timing of this acquired mutation is unknown.

DIAGNOSIS

The diagnostic criteria for neurofibromatosis-1, developed by the National Institutes of Health (NIH) Consensus Conference in 1987, are based on clinical findings and require 2 or more of the following: 6 or more CALMs $>$ 5 mm in prepubertal children or $>$ 15 mm in postpubertal patients, 2 or more of any type of neurofibroma or 1 plexiform neurofibroma, axillary or inguinal freckling, 2 or more Lisch nodules of the iris, a distinct bony lesion, an optic nerve glioma, or a first-degree relative with neurofibromatosis-1.[8,16] The hallmark features of the disorder are CALMs and neurofibromas.

The NIH criteria are highly sensitive and specific in all age groups except in young children. Because the clinical manifestations of neurofibromatosis-1 increase with age, many young children do not show enough features to meet the NIH diagnostic criteria. A definitive diagnosis can usually be made by age 4. One study by DeBella et al[17] showed that 97% of children older than 8 met the diagnostic criteria, but children under 8 years old often do not; therefore, these criteria may need to be modified for children in this age group. On the other hand, children with an affected parent can often be diagnosed within the first year of life because these patients only need to express one feature of neurofibromatosis-1 to be diagnosed.

In certain cases, genetic testing is necessary for diagnosis. Examples are a person who does not meet the clinical criteria but for whom clinicians have a high clinical suspicion, a young child with a serious tumor where a diagnosis of neurofibromatosis-1 would change management, or a case in which other differential diagnoses must be excluded.[6] Because of the vast number of mutations and the large size of the gene, genetic testing is complex and a negative test does not rule out neurofibromatosis-1. Nonetheless, the causative mutation can be found in 95% of patients who meet the clinical criteria for the disorder.[11]

Prenatal genetic testing via amniocentesis or chorionic villus sampling can be performed; however, the severity of the disease cannot be predicted.[6] Preimplantation genetic diagnosis by linkage analysis is a possibility for families with a known NF1 mutation. This method can select embryos that are unlikely to carry the NF1 mutation.[12]

A limitation to NF1 genetic testing is the inability to make an association between the genotype and the phenotype of the disease. In other words, identifying the genotype does not provide clues as to how mild or severe the disease will be. To date, only 2 genotype-phenotype correlations are known. One involves multiple microdeletions of the whole NF1 gene and is associated with severe disease, such as early-appearing and numerous neurofibromas, severe cognitive abnormalities, abnormal facial features, and an increased risk of developing malignant peripheral nerve sheath tumors.[10,13] This correlation

occurs in about 5% of neurofibromatosis-1 patients. The other known correlation is a 3-base pair in-frame deletion of exon 17. These patients exhibit CALMs and Lisch nodules without the presence of tumors.[6] The reason this form of neurofibromatosis-1 is milder may be secondary to the deletion of only a single amino acid rather than the creation of a truncated protein.[11]

Genetic counseling is important because of the autosomal dominant inheritance for the NF1 mutation, meaning that only 1 copy of the gene is needed for the disorder to develop. An NF1-heterozygous individual has a 50% chance of passing the disease to his or her offspring.[8] Of note, clinicians and researchers have not identified any individuals homozygous for NF1, and mice studies show that homozygous mice die in utero.[13] Because of variable expressivity, clinicians often diagnose a parent with neurofibromatosis-1 only after the child has been diagnosed. A parent may have few or no signs of neurofibromatosis-1, while the child may exhibit many features of the disease, or vice versa. The parents of a child diagnosed with the disorder should be thoroughly examined for the disease with a complete skin and ophthalmologic examination. If the parents show no signs of the disease, then the child's neurofibromatosis-1 resulted from a new mutation. In such a case, the chances of the parents having another child with neurofibromatosis-1 are low but still higher than those of the general population because of the possibility of gonadal mosaicism.[12]

The differential diagnosis of neurofibromatosis-1 includes other diseases that display similar features. Genetic testing may be required to rule out neurofibromatosis-1. Segmental neurofibromatosis-1 is a form of the disease in which patients exhibit features of neurofibromatosis-1 but in a limited anatomic area. This form of neurofibromatosis-1 is caused either by chance or by somatic mosaicism (some somatic cells have the mutation, while others do not). Legius syndrome, also known as neurofibromatosis-1–like syndrome, is an autosomal dominant syndrome caused by a mutation in the SPRED1 gene and is characterized by the presence of CALMs, axillary freckling, and macrocephaly. Patients with Legius syndrome lack Lisch nodules, neurofibromas, and central nervous system (CNS) tumors. Familial multiple café-au-lait spots are an autosomal dominant disorder in which patients have many CALMs without any other symptoms. These patients have not proven to be at risk for the development of neurofibromatosis-1.[10] Patients with certain homozygous hereditary nonpolyposis colorectal cancer mutations can express multiple CALMs, axillary freckling, cutaneous neurofibromas, and gastrointestinal (GI) malignancy. Other differential diagnoses to consider include McCune-Albright syndrome, LEOPARD syndrome, Turcot syndrome, congenital generalized fibromatosis, Proteus syndrome, multiple lipomatosis, and Bannayan-Riley-Ruvalcaba syndrome.[10-12]

CLINICAL MANIFESTATIONS

The clinical manifestations of neurofibromatosis-1 usually appear in a certain order as age increases. The typical order of appearance of the most common features is as follows: CALMs, axillary freckling, Lisch nodules, and neurofibromas. Other features include generalized hyperpigmentation, tumors, skeletal abnormalities, neurologic abnormalities, vasculopathies, and cardiac abnormalities. We discuss each of these manifestations below. The pathoetiology of the different clinical manifestations of the disease is very complex. Evidence shows that numerous mechanisms and cell-to-cell interactions are involved, and different theories are currently being studied.

Cutaneous Findings

CALMs are hyperpigmented, flat, well-demarcated lesions of the skin that arise during the first year of life in approximately 95% of neurofibromatosis-1 patients. These macules increase in both size and number with age.[8] The number of these lesions stabilizes over time, and the lesions tend to fade in older adults and the elderly. Patients without neurofibromatosis-1 may exhibit 3 or fewer of these macules; however, the presence of 6 or more is highly suggestive of the disease.[11] Current evidence shows the pathoetiology behind CALMs to be the presence of a mutation in both copies of the NF1 gene in melanocytes, resulting in giant melanosomes and increased melanin.[18] Freckling, or Crowe sign, usually appears by 4 years of age and most commonly occurs in the axillary and inguinal regions but can occur in any intertriginous region.[18] Although 90% of adults will exhibit freckling, CALMs and freckling do not normally have detrimental implications. However, some patients are psychologically affected by their appearance.

Generalized hyperpigmentation has been noted in neurofibromatosis-1 patients but has not been extensively studied. Research on melanocytes from hyperpigmented skin shows the presence of only one mutation in the NF1 gene.[10]

Ophthalmologic Findings

Lisch nodules are raised hamartomas of the iris that are sometimes pigmented. These nodules are not present at birth, but they increase in frequency with age and are present in more than 90% of neurofibromatosis-1 patients at 16 years old. They do not affect

vision. The slit-lamp ophthalmoscopic examination is the best method for finding these lesions.[11]

Another ophthalmologic finding, optic glioma, is discussed below with tumors.

Tumors

The neurofibroma is the most prevalent tumor associated with neurofibromatosis; however, the actual numbers of these fibromas vary among individuals and families.[8,19] A neurofibroma is a benign mass of the peripheral nerve or nerve root that consists of Schwann cells, fibroblasts, perineurial cells, and mast cells.[20] Neurofibromas can grow focally or spread along the length of the nerve.[21] These tumors most commonly form in the skin but can grow anywhere in the peripheral nervous system and can involve any organ. As stated previously, the pathoetiology behind the formation of these tumors is a second-hit mutation to the normal NF1 allele in Schwann cells. The classification of neurofibromas is controversial, but generally the classes include cutaneous, subcutaneous, and plexiform.

The most common type, with a prevalence of approximately 95%, is the cutaneous, or dermal, neurofibroma. This tumor type forms in the dermis and arises from peripheral nerves.[22] These soft, fleshy, dome-shaped tumors appear around adolescence and increase in both size and number with age, with a tendency to cluster over the trunk.[11] Cutaneous neurofibromas are often pruritic, painful, and cosmetically unappealing, but no diagnostic evidence indicates that cutaneous neurofibromas undergo a malignant evolution.[8,19] These tumors increase in size and number during pregnancy, suggesting that they may be hormone responsive.[23] Conversely, neurofibromas do not seem to increase in size with the use of hormonal contraception.[24]

Subcutaneous neurofibromas are firm, tender nodules that appear around adolescence/early adulthood. The plexiform neurofibroma, present in about half of neurofibromatosis-1 patients, involves multiple nerve fascicles rather than just one nerve. Considered congenital lesions, most of these neurofibromas are internal and often not visible during infancy. Infants may exhibit an area of hyperpigmentation or hypertrichosis over the spot where a future lesion will develop. These lesions are usually not suspected until they become symptomatic or disfiguring.[12] Plexiform neurofibromas can cause complications such as pain, nerve root and spinal cord compression, and vertebral erosion.[19,22] Both subcutaneous and plexiform neurofibromas have the potential to transform into malignant peripheral nerve sheath tumors (MPNSTs).[25]

Another finding in neurofibromatosis-1 is the increased frequency of both benign and malignant tumors, other than neurofibromas, including MPNSTs, optic pathway gliomas, other CNS tumors, and non-CNS tumors. The overall risk of malignancy in neurofibromatosis-1 patients is 2.5 to 4 times more than that of the general population, but this increased risk applies only to brain and connective tissue tumors.[11,26] The overall risk of cancer at other sites is not increased.[26] Interestingly, the risk of cancer is higher in female neurofibromatosis-1 patients versus males.[26,27]

MPNSTs are the most frequent malignant neoplasm found in neurofibromatosis-1 patients. These aggressive tumors commonly form from the malignant transformation of a plexiform neurofibroma. They are difficult to detect and diagnose and often metastasize quickly to distant sites.[6] An 8% to 13% probability of the formation of MPNSTs exists over the lifespan of any neurofibromatosis-1 patient, with most of the high-grade lesions occurring in young adults.[12] These tumors often present as persistent pain in a neurofibroma, new or unexplained neurologic deficits, hardening of the neurofibroma, or a rapid increase in fibroma size.[6] Neurofibromatosis-1 patients treated with radiotherapy for an optic glioma seem to have a higher risk of developing an MPNST.[28] Evidence conflicts regarding whether patients with large NF1 gene deletions are more susceptible to developing MPNSTs.[29,30]

The most common CNS manifestation is the optic pathway glioma,[31] present in about 15% of neurofibromatosis-1 children younger than 6 years old. Most remain asymptomatic, but when symptomatic optic gliomas occur, they usually present by 3 years of age.[17] These tumors can arise from anywhere in the optic pathway and may cause visual field defects, vision loss, pupillary defects, and proptosis.[6] If the tumor involves the optic chiasm, the child may present with precocious or possibly delayed puberty. Symptomatic optic gliomas are usually stable or slow growing, and some may even spontaneously regress.[32] Routine screening for optic glioma includes annual ophthalmologic examinations; however, if a child presents with visual symptoms, proptosis, or abnormal puberty, the patient should undergo magnetic resonance imaging (MRI). Much controversy exists over whether to screen asymptomatic neurofibromatosis-1 patients with an MRI to allow for early detection and possible intervention.[33]

Other CNS neoplasms commonly found in neurofibromatosis-1 are astrocytomas and brainstem or cerebellar gliomas. Patients with optic gliomas, especially those patients who were treated with radiotherapy, are at a particularly higher risk for

developing these CNS neoplasms.[34] Fortunately, brain tumors in neurofibromatosis-1 patients tend to have a more benign course than brain tumors in the general population.[12]

Non-CNS tumors that have a higher incidence in neurofibromatosis-1 patients include rhabdomyosarcomas, gastrointestinal stromal tumors (GISTs), pheochromocytomas, carcinoid tumors, ganglioneuromas, and certain myeloid leukemias, especially juvenile myelomonocytic leukemia (JMML).[35,36] Burgdorf and Zelger[37] reported a 200- to 500-fold increased risk of JMML in neurofibromatosis-1 patients. Multiple other studies have suggested that these patients may have an increased incidence of breast cancer; however, data conflict.[11] For example, a study by Sharif et al[38] reported that women with neurofibromatosis-1 have a 3.5-fold increased risk of developing breast cancer. Another study by Walker et al[27] showed that neurofibromatosis-1 patients might have an increased risk for early-onset breast cancer (women under the age of 50). However, Airewele at al[26] reported that even though the total cancer incidence is higher in patients with neurofibromatosis-1, the incidence of common cancers (eg, breast, colon, and prostate cancer) was not increased. The associations between neurofibromatosis-1 and malignant cancers are still being investigated.

Skeletal Findings

The skeletal abnormalities often seen in neurofibromatosis-1 patients include pseudarthroses, bone lesions, scoliosis, osteoporosis, short stature, macrocephaly, prominent brow and forehead, and pectus excavatum. The mechanism behind these abnormalities is not well understood, but the deficiency of osteoblasts with the increased survival of osteoclasts may play a role.[39] Pseudarthrosis, a false joint, often forms secondary to impaired bone healing at sites of bone dysplasia. Long bone pseudarthrosis occurs in about 5% of neurofibromatosis-1 infants and usually presents as tibial bowing with subsequent cortical thinning and fracture, usually by age 2.[11,35,40] Neurofibromatosis-1 bone lesions include dysplasia or cortical thinning of long bones, scalloping of the vertebrae, and sphenoid wing dysplasia. Scoliosis, which may occur as a result of osteopenia or bony dysplasia,[39] is found in 10%-25% of neurofibromatosis-1 patients and usually becomes apparent during early childhood/adolescence.[8,14] More uncommon, though significant, kyphoscoliosis is associated with tumors and a higher than normal neurologic deficit.[41] Neurofibromatosis-1 may also lead to a gradual degradation of the rib cage, producing a flail chest; however, this is uncommon. Osteopenia and osteoporosis are common findings in neurofibromatosis-1 patients. The etiology is unknown, and in one small trial the use of calcium and vitamin D did not seem to improve bone density.[11,12]

Neurologic Findings

Neurologic abnormalities include cognitive deficits, specific learning disabilities, attention deficit hyperactivity disorder (ADHD), seizures, macrocephaly, peripheral neuropathy, headaches, and aqueductal stenosis.[42] Neurofibromatosis-1 patients often have an intelligence quotient (IQ) about 5 to 10 points below that of the general population; however, the incidence of intellectual disability (IQ $<$ 70) is only slightly higher than that of the general population. Specific learning disabilities occur in 50%-75% of patients with the disorder, commonly involving problems with math and reading, visual spatial construction, memory, and articulation.[8] Additionally, ADHD is seen in 39% of these patients, and many have poorer social skills than the general population. Seizure prevalence is approximately twice as high as that of the general population.

Macrocephaly, a head circumference greater than or equal to 2 standard deviations above the mean, is found in 25%-50% of neurofibromatosis-1 patients secondary to increased brain volume. This problem may be associated with the cognitive deficits evident in patients with the disorder. Peripheral neuropathy as a result of nerve and spinal root compression can occur but is more common in patients with neurofibromatosis type 2 (incidence of 3% and 50%, respectively).[11] Patients who experience this form of neuropathy often have significant pain. Headaches are another common complaint among neurofibromatosis-1 patients. Occasionally, patients may have aqueductal stenosis and hydrocephalus. On neuroimaging via MRI, neurofibromatosis-associated bright spots, or unidentified bright objects (UBOs), are seen in 60% of patients. UBOs often occur in the basal ganglia, cerebellum, brainstem, and subcortical white matter and are thought to be increased fluid within the myelin. Data conflict regarding whether the UBOs are associated with intellectual impairment. Moreover, the UBOs are not associated with focal neurologic deficits or mass effect and tend to go away with age.[11,12]

Vasculopathy

Neurofibromatosis-1–associated vasculopathies include stenoses, aneurysms, and arteriovenous malformations involving the aortic, renal, mesenteric, carotid-vertebral, subclavian-axillary, iliofemoral, intracerebral, and coronary arteries.[43,44] Several studies provide evidence that a neurofibromin deficiency in the vessel endothelial and smooth muscle cells is the likely pathogenesis of neurofibromatosis-1–associat-

ed vasculopathy. Lasater et al[45] showed that neurofibromin is important for vessel homeostasis through its regulation of interactions between bone marrow–derived cells and endothelial and smooth muscle cells after vessel injury. A deficiency of neurofibromin in these cells results in poor homeostasis, vascular inflammation, and cellular proliferation.[45] Initially, researchers believed that the process involved Schwann cell proliferation with a secondary fibrosis forming on the vessel wall[46,47]; however, more recent studies have shown that smooth muscle cells actually proliferate instead of Schwann cells.[48]

Another proposed mechanism for neurofibromatosis-1–associated vasculopathy is that neurofibromin in the vessel wall may work to suppress smooth muscle cell proliferation.[49-51] Interestingly, the arterial distribution of neurofibromatosis-1–associated vasculopathy is similar to the distribution seen in atherosclerosis, suggesting that blood flow velocity may also contribute to the development of these lesions.[49] Furthermore, analysis of peripheral blood from patients with neurofibromatosis-1 has revealed increased levels of inflammatory cells and cytokines, which previously had been linked to the development of atherosclerosis and, therefore, may contribute to the vasculopathy.[45] The vasculopathy affects both the cerebrovascular and the cardiovascular systems.[43] Stenoses in the brain can result in the formation of small telangiectatic vessels around the areas of occlusion, known as moyamoya. These occlusions can result in symptomatic ischemic disease and possibly predispose patients with these occlusions to stroke.

Hypertension is another common cardiovascular finding that may present at any age.[43] The most common etiology is essential hypertension; however, young neurofibromatosis-1 patients with hypertension are most likely hypertensive secondary to renal artery stenosis. Other causes of hypertension include pheochromocytoma and coarctation of the aorta.[2,12,52]

Cardiac Findings

The increased incidence of heart defects has long been debated.[44,53,54] Neurofibromin has been found to be vital in the development of the heart in mice. Mouse embryos with a homozygous mutation of the NF1 gene die early in gestation from heart defects.[8] In 2002, an echocardiography study of 48 neurofibromatosis-1 patients showed the presence of a cardiac abnormality in 13 of the 48 subjects (27%).[54] The abnormalities included atrial septal defects, atrial septal aneurysms, pulmonary stenosis, coarctation of the aorta, mitral valve prolapse, mitral regurgitation, aortic regurgitation, and hypertrophic cardiomyopathy. The investigators recommended that regular cardiovascular examinations, including echocardiography, be performed in all neurofibromatosis-1 patients.[54] Proposed mechanisms for the presence of hypertrophic cardiomyopathy and outflow obstruction in association with neurofibromatosis-1 include neurofibroma formation in the heart or septal hypertrophy secondary to abnormal catecholamine metabolism in these patients. Conversely, these 2 conditions may coexist because of a common hereditary defect in neural crest tissue.[42,55] The association between neurofibromatosis-1 and cardiomyopathy is still debated.

MULTISYSTEMIC COMPLICATIONS AND CONSIDERATIONS OF ANESTHESIA

Neurofibromatosis-1 has the potential for serious medical problems involving every major anatomical system. A breakdown in symptom presentation and associated complications follows, arranged in accordance with the involved anatomical system. Complications that may pose a threat during surgery and anesthesia are also discussed.

Central Nervous System

Neurofibromatosis-1 has multiple effects on the CNS, as discussed above. Tumors within the CNS often necessitate brain or spinal neurosurgery. The anesthetic considerations for this type of surgery are similar to those for standard neural surgery. Tumors of the brainstem may result in central hypoventilation syndrome that often requires prolonged weaning from mechanical ventilation.[42] Neurofibromatosis-1–associated vasculopathy can involve the carotid and intracerebral arteries, resulting in stenoses and/or aneurysms of these vessels that can be problematic during surgery and anesthesia. Perioperatively, anesthesiologists must maintain careful control of arterial pressure in case of vasculopathy that imposes a risk for aneurysm rupture and stroke.[42] The literature reports a case of fatal neurogenic pulmonary edema in a child undergoing spinal surgery.[56] This case highlights the importance of careful, preemptive management of neurofibromatosis-1 patients during surgery. Anesthesiologists must consider the higher incidence of epilepsy and the possibility of an undiagnosed brain tumor and of severe hemorrhage during the removal of a plexiform neurofibroma. Additionally, a postoperative neurologic examination is warranted to ensure that the patient has returned to his or her preexisting neurologic status.

Respiratory System

Neurofibromas can be present in the tongue, larynx, trachea, or bronchi and can result in blockage of the airway and interference with intubation, as reported in several cases.[57,58] Patients may present

with a coarse voice, difficulty swallowing, or deviated trachea. These tumors impose substantial risk and complicate anesthetic management during surgery. A successful and uneventful endotracheal neurofibroma removal reported by Chen et al[58] combined mild anesthesia and fiberoptic bronchoscopy to assist with endotracheal intubation. Another successful intratracheal mass removal used rapid induction intubation.[57] Both case reports of endotracheal tumor removal discuss having an extracorporeal membrane oxygenation system on standby in case of any complications during the procedure. Additionally, the use of a tube 0.5 to 1 cm smaller than normal should be considered to help bypass the mass.[57,58]

Neurofibromas can also pose a challenge to the anesthesiologist when they occur in the nasal, sinus, or maxillofacial cavities.[40] Another complication involving the respiratory system is the possibility of chest wall deformities secondary to scoliosis and kyphoscoliosis that can cause a reduction in lung volume and breathing capacity and may ultimately lead to respiratory compromise or failure.[6,59] In the past, parenchymal lung disease and neurofibromatosis-1 were linked in theory, but this association is now believed to be caused by multiple confounders and has since been discarded.[60,61] For patients with neurofibromatosis-1, the preoperative evaluation should include pulmonary function testing, examination via indirect laryngoscopy, and computed tomography (CT) or MRI to investigate for any respiratory complications and to plan the proper anesthetic technique.[42]

Cardiovascular System

Cardiovascular complications include hypertension, vasculopathy, cardiomyopathy, heart defects (all discussed above), and superior vena cava obstruction. Mediastinal neurofibromas have been well documented as causing superior vena cava compression. El Oakley and Grotte[40] reported the case of a 21-year-old female patient with a familial history of neurofibromatosis-1 and progressive shortness of breath while at rest. Chest x-ray revealed a mediastinal mass that was causing superior vena cava and tracheal compression. A biopsy determined that the mass was a neurofibroma.[40] From an anesthesia perspective, vena cava compression may decrease preload to the heart and cause severe hypotension during surgery. Also, such patients may not respond to fluid resuscitation as quickly as patients without obstructions. If obstruction is suspected, it may be prudent to obtain a preoperative CT scan or chest x-ray to determine the site and extent of the obstruction and to plan accordingly with proper induction agents and volume.

Both pheochromocytomas and carcinoid tumors can cause detrimental changes in blood pressure. The administration of beta-blockers for blood pressure control can precipitate a hypertensive crisis and death if a pheochromocytoma is present.[42] To be best prepared for possible cardiovascular complications in a neurofibromatosis-1 patient, preoperative recommendations include careful questioning about cardiovascular disease, reviewing prior echocardiography reports, performing blood pressure measurements to screen for hypertension, and cautiously using nephrotoxic drugs only if absolutely necessary. During surgery, anesthesiologists must pay close attention to the heart rhythm and blood pressure and maintain a high index of suspicion for the possibility of pheochromocytoma and carcinoid tumors.

Musculoskeletal System

As discussed previously, the musculoskeletal complications of neurofibromatosis-1 include pseudarthroses, bone lesions, scoliosis, kyphoscoliosis, and osteoporosis. The presence of scoliosis, kyphoscoliosis, or spinal cord tumors can make the use of spinal or epidural anesthesia challenging for an anesthesiologist.[42] In neurofibromatosis-1 patients, spinal cord neurofibromas should be ruled out by CT or MRI before epidural or spinal procedures are performed.[62]

Gastrointestinal and Genitourinary Systems

Tumors are the main GI manifestation of neurofibromatosis-1 and most commonly include neurofibromas, MPNSTs, ganglioneuromas, GISTs, pheochromocytomas, and carcinoid tumors.[63] GI tumors may present with abdominal pain, abnormal gut motility, hematemesis, or melena. These tumors can result in certain complications, such as obstruction, perforation, hemorrhage, and hypertension. In neurofibromatosis-1 patients, it is very important to thoroughly explore the abdominal cavity to detect any undiagnosed GI tumors. Early diagnosis and treatment of these tumors prevent complications and possible death from malignancy.

Neurofibromas may share a common neuroendocrine origin with carcinoid tumors and pheochromocytomas. These 3 types of tumors can occur together.[64] The manifestations of both pheochromocytomas and carcinoid tumors are hazardous in surgical settings, as seen in the general population. Surgical removal of pheochromocytomas can result in hypertensive crisis, cardiac arrhythmias, and multiorgan dysfunction. The management of these patients is via administration of an alpha-antagonist (phenoxybenzamine) days before surgery with the addition of a beta-blocker (propranol) after the initiation of the alpha-antagonist. Intraoperative processes should

include continuous monitoring of intraarterial pressure and heart rhythm, as well as adequate volume restoration to prevent postoperative hypotension.[65,66] Intraoperative complications of carcinoid tumor removal include potentially fatal hypotension, cardiac arrhythmias, and bronchoconstriction. Successful anesthetic management involves the use of preoperative and intraoperative octreotide.[67-69] Neurofibromatosis-1 patients with either of these tumor types should undergo duodenal imaging to exclude the presence of a coexisting tumor.[42]

Neurofibromas in the retroperitoneal and pelvic regions may cause ureteric or urethral obstruction and result in hydronephrosis. These tumors may pose difficulty for catheterization.

Pregnancy

Pregnancy in patients with neurofibromatosis-1 can result in multiple complications. During pregnancy, hypertension may be exacerbated, neurofibromas may increase in size, and large pelvic or genital neurofibromas may cause preterm labor or complicate delivery.[12,42] A study by Segal et al[70] showed a significantly higher rate of intrauterine growth restriction, stillbirths, and the need for cesarean sections in pregnant women with neurofibromatosis-1. Additionally, the increase in neurofibroma size may cause an increase in intracranial pressure. According to Dounas et al,[62] the presence of increased intracranial pressure and spinal neurofibromas should be evaluated using CT or MRI before spinal or epidural anesthesia despite the radiation risk to the fetus. Regarding anesthetic management during labor and delivery, the anesthesiologist must consider the possibility of increased intracranial pressure, spinal abnormalities, and spinal tumors that can complicate regional anesthesia.[42]

Medications Used During Anesthesia

In the past, patients with neurofibromatosis-1 were thought to be more sensitive to neuromuscular blocking agents, but research has disproven this theory.[42,71] Even so, anesthesiologists should use these drugs with caution and monitor neuromuscular transmission throughout surgery because of the risk of renal impairment from renal artery stenosis in these patients. Beta-blockers should also be used with caution in these patients because of the possibility of an undiagnosed pheochromocytoma.

MANAGEMENT

Upon initial diagnosis, physicians should obtain a thorough history and physical examination to establish disease extent. The important components of the history are personal and family medical history, developmental assessment, and school performance. The important aspects of the physical examination are ophthalmologic, skin, skeletal, cardiovascular, and neurologic assessments. Examinations should also include the parents and siblings of newly diagnosed patients. Routine MRI at the time of diagnosis is controversial. The MRI may be helpful in diagnosing neurofibromatosis-1 and in finding brain lesions earlier; however, such diagnoses often do not change clinical management. Also, brain lesions can develop at any time throughout life, so a negative MRI does not exclude future complications. Regardless, if a patient has neurologic symptoms or symptoms that are indicative of an optic glioma, MRI is necessary.

The treatment of neurofibromatosis-1 focuses on symptom management. Pigmentary changes can be treated with several methods, such as avoiding the sun, applying sunscreen, wearing cover-up clothing, and possibly using topical vitamin D3 and laser therapy.[10] Disfiguring and symptomatic cutaneous neurofibromas can be surgically removed. Treatment for the plexiform type of neurofibroma is unclear, and studies are limited. Surgical resection is extremely complicated because of the tumor's invasiveness, vascularity, and proximity to the nerve. These tumors can usually only be partially resected and usually recur. One study on the treatment of testicular seminomas showed that carboplatin might be beneficial in reducing the plexiform tumor's size.[72] However, one must consider the high risk of secondary malignancy in patients with neurofibromatosis-1. Ongoing clinical trials are testing tipifarnib, imatinib, sirolimus, antiangiogenic agents, and other drugs for treatment of these tumors.[10,11] A list of the current trials can be found at www.clinicaltrials.gov.

Possible approaches to optic gliomas include no treatment for nonprogressive, asymptomatic optic gliomas or chemotherapy if the gliomas are progressive and symptomatic.

The best treatment of MPNSTs is complete excision. Adjuvant radiation and chemotherapy have unclear success rates. Neurofibromatosis-1 patients with MPNSTs have a 5-year survival rate of approximately 21%.[19] Radiotherapy is problematic in patients with neurofibromatosis-1 because it can result in the development of MPNSTs, brain tumors, and moyamoya.[12] Bracing or surgery can be used to treat scoliosis. In regard to the impaired cognitive function, one study has reported improved cognitive function in a neurofibromatosis-1 mouse model through the use of lovastatin.[32] Lovastatin functions not only as a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, but also as an inhibitor of Ras.[10] Current trials are using statins to help improve cognitive functioning in humans with neurofibromatosis-1. Medications may

treat coexisting ADHD, depression, or anxiety. The management of hypertension in these patients involves removing the cause. Modalities include the use of medications for essential hypertension, percutaneous angioplasty or bypass surgery for renal artery stenosis, and tumor removal for pheochromocytomas. Corrective surgeries for renal artery stenosis in patients with neurofibromatosis-1 have demonstrated mixed results; however, percutaneous angioplasty has shown promise in reducing symptoms.[42,73]

Specialists should follow patients with neurofibromatosis-1 regularly to monitor the skin, eyes, CNS, skeletal system, and cardiovascular system. All patients with the disease should have an annual physical examination with blood pressure readings. Children and adolescents should also have annual growth assessments, including height, weight, and head circumference plotted on a growth chart; annual ophthalmologic evaluations; and annual developmental assessments. Ophthalmologic examinations should be performed annually until age 8, biannually until age 18, and less frequently in adulthood. Patients with neurofibromatosis-1 have no limitations on physical activity unless required secondary to skeletal complications.[12,74] The life expectancy of these patients appears to be shortened by about 15 years. The most common causes of death are from MPNSTs, CNS tumors, and vasculopathy.[12,75]

In recent years, a better understanding of the genetics involved with this complicated disorder has provided hope for better treatments in the future. Mapping the mutations is a way to understand the disease and drive researchers to examine the mutations, locate the regions within the chromosome where they are most likely to be found, and find treatments to suppress or reverse these mutations.[2]

CONCLUSIONS

Neurofibromatosis-1 is not only a neurocutaneous disorder but also a multisystemic disorder with multifaceted implications throughout nearly every organ system in the human body. Patients with the disease require follow-up and management by multiple disciplines throughout the course of their lives. The study of neurofibromatosis-1 is ongoing. Current research is focusing on genotype-phenotype correlations, investigation of the pathoetiology behind the various clinical manifestations of the disease, and the search for treatment options for the different features of neurofibromatosis. Furthermore, new cancer and other systemic associations are continuously being found. Neurofibromatosis-1 has proven to be a very complex yet intriguing syndrome about which an immense amount of information remains undiscovered.

Anesthesiologists must perform a thorough preoperative evaluation of every patient and have a well-formed and comprehensive anesthetic plan to be prepared for any complications that may occur. However, in patients with neurofibromatosis-1, anesthesiologists face additional complications and obstacles that they must consider when devising an anesthetic plan. Neurofibromatosis-1–associated complications of the central nervous, respiratory, cardiovascular, musculoskeletal, and GI and genitourinary systems all present various degrees of considerations for the anesthesiologist. The disease also has dramatic implications for pregnant women. Additionally, certain drugs must be used with caution. The anesthesiologist must consider the possibility of each of the multisystemic complications when evaluating and managing the patient for surgical procedures.

REFERENCES

1. National Institute of Neurological Disorders and Stroke. Neurofibromatosis Fact Sheet. May 2011. http://www.ninds.nih.gov/disorders/neurofibromatosis/detail_neurofibromatosis.htm. Accessed 16 March 2012.
2. Mulvihill JJ, Parry DM, Sherman JL, Pikus A, Kaiser-Kupfer MI, Eldridge R. NIH conference. Neurofibromatosis 1 (Recklinghausen disease) and neurofibromatosis 2 (bilateral acoustic neurofibromatosis). An update. *Ann Intern Med*. 1990 Jul 1;113(1):39-52.
3. Nussbaum R, McInnes R, Willard HF. *Thompson & Thompson Genetics in Medicine*. Philadelphia, PA: W.B. Saunders; 2007: 119-120, 292-293.
4. Cawthon RM, O'Connell P, Buchberg AM, et al. Identification and characterization of transcripts from the neurofibromatosis 1 region: the sequence and genomic structure of EVI2 and mapping of other transcripts. *Genomics*. 1990 Aug;7(4):555-565.
5. Wallace MR, Marchuk DA, Andersen LB, et al. Type 1 neurofibromatosis gene: identification of a large transcript disrupted in three NF1 patients. *Science*. 1990 Jul 13;249(4965): 181-186. Erratum in: *Science*. 1990 Dec 21;250(4988):1749.
6. Friedman JM. Neurofibromatosis 1. GeneReviews, NCBI Bookshelf. June 2, 2009. http://www.ncbi.nlm.nih.gov/books/NBK1109/#nfl.genetic_Counseling. Accessed 2 October 2010.
7. Feldkamp MM, Angelov L, Guha A. Neurofibromatosis type 1 peripheral nerve tumors: aberrant activation of the Ras pathway. *Surg Neurol*. 1999 Feb;51(2):211-218.
8. Ferner RE. Neurofibromatosis 1 and neurofibromatosis 2: a twenty first century perspective. *Lancet Neurol*. 2007 Apr;6(4):340-351.
9. Passarge E. *Color Atlas of Genetics*. Stuttgart, Germany: Georg Thieme Publishers; 2007:338-339.
10. Boyd KP, Korf BR, Theos A. Neurofibromatosis type 1. *J Am Acad Dermatol*. 2009 Jul;61(1):1-14; quiz 15-16.
11. Plon SE, Blazo M. Neurofibromatosis type 1 (von Recklinghausen's disease). UpToDate. Waltham, MA: Wolters Kluwer Health; 2011. http://www.uptodate.com. Accessed 8 March 2012.
12. Jett K, Friedman JM. Clinical and genetic aspects of neurofibromatosis 1. *Genet Med*. 2010 Jan;12(1):1-11.
13. Jouhilahti EM, Peltonen S, Heape AM, Peltonen J. The pathoetiology of neurofibromatosis 1. *Am J Pathol*. 2011 May; 178(5):1932-1939. Epub 2011 Mar 31.

14. Ars E, Kruyer H, Morell M, et al. Recurrent mutations in the NF1 gene are common among neurofibromatosis type 1 patients. *J Med Genet*. 2003 Jun;40(6):e82.
15. Stephens K, Kayes L, Riccardi VM, Rising M, Sybert VP, Pagon RA. Preferential mutation of the neurofibromatosis type 1 gene in paternally derived chromosomes. *Hum Genet*. 1992 Jan;88(3): 279-282.
16. Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. *Arch Neurol*. 1988 May;45(5):575-578.
17. DeBella K, Szudek J, Friedman JM. Use of the National Institutes of Health criteria for diagnosis of neurofibromatosis 1 in children. *Pediatrics*. 2000 Mar;105(3 Pt 1):608-614.
18. De Schepper S, Maertens O, Callens T, Naeyaert JM, Lambert J, Messiaen L. Somatic mutation analysis in NF1 café au lait spots reveals two NF1 hits in the melanocytes. *J Invest Dermatol*. 2008 Apr;128(4):1050-1053. Epub 2007 Oct 4.
19. Le LQ, Shipman T, Burns DK, Parada LF. Cell of origin and microenvironment contribution for NF1-associated dermal neurofibromas. *Cell Stem Cell*. 2009 May 8;4(5):453-463.
20. Kumar V, Cotran RS, Robbins SL, eds. *Basic Pathology*. Philadelphia, PA: W.B. Saunders; 1997:189-190.
21. Ling BC, Wu J, Miller SJ, et al. Role for the epidermal growth factor receptor in neurofibromatosis-related peripheral nerve tumorigenesis. *Cancer Cell*. 2005 Jan;7(1):65-75.
22. Carroll SL, Ratner N. How does the Schwann cell lineage form tumors in NF1? *Glia*. 2008 Nov 1;56(14):1590-1605.
23. Gutmann DH. Recent insights into neurofibromatosis type 1: clear genetic progress. *Arch Neurol*. 1998 Jun;55(6):778-780.
24. Lammert M, Friedman JM, Roth HJ, et al. Vitamin D deficiency associated with number of neurofibromas in neurofibromatosis 1. *J Med Genet*. 2006 Oct;43(10):810-813. Epub 2006 Mar 29.
25. Tucker T, Wolkenstein P, Revuz J, Zeller J, Friedman JM. Association between benign and malignant peripheral nerve sheath tumors in NF1. *Neurology*. 2005 Jul 26;65(2):205-211.
26. Airewele GE, Sigurdson AJ, Wiley KJ, et al. Neoplasms in neurofibromatosis 1 are related to gender but not to family history of cancer. *Genet Epidemiol*. 2001 Jan;20(1):75-86.
27. Walker L, Thompson D, Easton D, et al. A prospective study of neurofibromatosis type 1 cancer incidence in the UK. *Br J Cancer*. 2006 Jul 17;95(2):233-238. Epub 2006 Jun 20.
28. Kleinerman RA. Radiation-sensitive genetically susceptible pediatric sub-populations. *Pediatr Radiol*. 2009 Feb;39 Suppl 1: S27-S31. Epub 2008 Dec 16.
29. Kluwe L, Friedrich RE, Peiper M, Friedman J, Mautner VF. Constitutional NF1 mutations in neurofibromatosis 1 patients with malignant peripheral nerve sheath tumors. *Hum Mutat*. 2003 Nov; 22(5):420.
30. Upadhyaya M, Spurlock G, Majounie E, et al. The heterogeneous nature of germline mutations in NF1 patients with malignant peripheral serve sheath tumours (MPNSTs). *Hum Mutat*. 2006 Jul;27(7):716.
31. Spiro SG. Lung tumours. In: Brewis RAL, Gibson GJ, Geddes DM, eds. *Respiratory Medicine*. London, UK: Balliere Tindall; 1990: 874.
32. Li W, Cui Y, Kushner SA, et al. The HMG-CoA reductase inhibitor lovastatin reverses the learning and attention deficits in a mouse model of neurofibromatosis type 1. *Curr Biol*. 2005 Nov 8; 15(21):1961-1967.
33. Listernick R, Ferner RE, Liu GT, Gutmann DH. Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. *Ann Neurol*. 2007 Mar;61(3):189-198.
34. Friedman JM, Birch P. An association between optic glioma and other tumours of the central nervous system in neurofibromatosis type 1. *Neuropediatrics*. 1997 Apr;28(2):131-132.
35. Seif AE. Pediatric leukemia predisposition syndromes: clues to understanding leukemogenesis. *Cancer Genet*. 2011 May;204(5): 227-244.
36. Andersson J, Sihto H, Meis-Kindblom JM, Joensuu H, Nupponen N, Kindblom LG. NF1-associated gastrointestinal stromal tumors have unique clinical, phenotypic, and genotypic characteristics. *Am J Surg Pathol*. 2005 Sep;29(9):1170-1176.
37. Burgdorf WH, Zelger B. JXG, NF1, and JMML: alphabet soup or a clinical issue? *Pediatr Dermatol*. 2004 Mar-Apr;21(2):174-176.
38. Sharif S, Moran A, Huson SM, et al. Women with neurofibromatosis 1 are at a moderately increased risk of developing breast cancer and should be considered for early screening. *J Med Genet*. 2007 Aug;44(8):481-484. Epub 2007 Mar 16.
39. Schindeler A, Little DG. Recent insights into bone development, homeostasis, and repair in type 1 neurofibromatosis (NF1). *Bone*. 2008 Apr;42(4):616-622. Epub 2007 Nov 28.
40. el Oakley R, Grotte GJ. Progressive tracheal and superior vena caval compression caused by benign neurofibromatosis. *Thorax*. 1994 Apr;49(4):380-381.
41. Tewari P, Pandey CK, Tyagi I. Retropharyngeal neurofibroma presenting with severe kypho-scoliosis: respiratory obstruction in postoperative period. *Can J Anaesth*. 2001 Apr;48(4):422-423.
42. Hirsch NP, Murphy A, Radcliffe JJ. Neurofibromatosis: clinical presentations and anaesthetic implications. *Br J Anaesth*. 2001 Apr;86(4):555-564.
43. Friedman JM, Arbiser J, Epstein JA, et al. Cardiovascular disease in neurofibromatosis 1: report of the NF1 Cardiovascular Task Force. *Genet Med*. 2002 May-Jun;4(3):105-111.
44. Oderich GS, Sullivan TM, Bower TC, et al. Vascular abnormalities in patients with neurofibromatosis syndrome type I: clinical spectrum, management, and results. *J Vasc Surg*. 2007 Sep; 46(3):475-484. Epub 2007 Jul 30.
45. Lasater EA, Li F, Bessler WK, et al. Genetic and cellular evidence of vascular inflammation in neurofibromin-deficient mice and humans. *J Clin Invest*. 2010 Mar 1;120(3):859-870. Epub 2010 Feb 15.
46. Rubinstein LJ. The malformative central nervous system lesions in the central and peripheral forms of neurofibromatosis. A neuropathological study of 22 cases. *Ann N Y Acad Sci*. 1986; 486:14-29.
47. Salyer WR, Salyer DC. The vascular lesions of neurofibromatosis. *Angiology*. 1974 Sep;25(8):510-519.
48. Ahlgren-Beckendorf JA, Maggio WW, Chen F, Kent TA. Neurofibromatosis 1 mRNA expression in blood vessels. *Biochem Biophys Res Commun*. 1993 Dec 15;197(2):1019-1024.
49. Hamilton SJ, Friedman JM. Insights into the pathogenesis of neurofibromatosis 1 vasculopathy. *Clin Genet*. 2000 Nov;58(5): 341-344.
50. Norton KK, Xu J, Gutmann DH. Expression of the neurofibromatosis I gene product, neurofibromin, in blood vessel endothelial cells and smooth muscle. *Neurobiol Dis*. 1995 Feb; 2(1):13-21.

51. Riccardi VM. Histogenesis control genes and neurofibromatosis 1. *Eur J Pediatr*. 2000 Jul;159(7):475-476.
52. Walther MM, Herring J, Enquist E, Keiser HR, Linehan WM. von Recklinghausen's disease and pheochromocytomas. *J Urol*. 1999 Nov;162(5):1582-1586.
53. Lin AE, Garver KL. Cardiac abnormalities in neurofibromatosis. *Neurofibromatosis*. 1988;1(3):146-151.
54. Tedesco MA, Di Salvo G, Natale F, et al. The heart in neurofibromatosis type 1: an echocardiographic study. *Am Heart J*. 2002 May;143(5):883-888.
55. Fitzpatrick AP, Emanuel RW. Familial neurofibromatosis and hypertrophic cardiomyopathy. *Br Heart J*. 1988 Sep;60(3):247-251.
56. Van Aken H, Scherer R, Lawin P. A rare intra-operative complication in a child with Von Recklinghausen's neurofibromatosis. *Anaesthesia*. 1982 Aug;37(8):827-829.
57. Dodge TL, Mahaffey JE, Thomas JD. The anesthetic management of a patient with an obstructing intratracheal mass: a case report. *Anesth Analg*. 1977 Mar-Apr;56(2):295-298.
58. Chen PT, Chang WK, Hsu WH, Sung CS, Chan KH, Tsai SK. Anesthetic management of a patient undergoing segmental resection of trachea with an endotracheal neurofibroma and nearly total occlusion of trachea. *Acta Anaesthesiol Taiwan*. 2004 Dec;42(4):233-236.
59. Riccardi VM, Eichner JE. *Neurofibromatosis: Phenotype, Natural History and Pathogenesis*. Baltimore, MD: Johns Hopkins University Press; 1986.
60. Ryu JH, Parambil JG, McGrann PS, Aughenbaugh GL. Lack of evidence for an association between neurofibromatosis and pulmonary fibrosis. *Chest*. 2005 Oct;128(4):2381-2386.
61. Webb WR, Goodman PC. Fibrosing alveolitis in patients with neurofibromatosis. *Radiology*. 1977 Feb;122(2):289-293.
62. Dounas M, Mercier FJ, Lhuissier C, Benhamou D. Epidural analgesia for labour in a parturient with neurofibromatosis. *Can J Anaesth*. 1995 May;42(5 Pt 1):420-422; discussion 422-424.
63. Basile U, Cavallaro G, Polistena A, et al. Gastrointestinal and retroperitoneal manifestations of type 1 neurofibromatosis. *J Gastrointest Surg*. 2010 Jan;14(1):186-194.
64. Wheeler MH, Curley IR, Williams ED. The association of neurofibromatosis, pheochromocytoma, and somatostatin-rich duodenal carcinoid tumor. *Surgery*. 1986 Dec;100(6):1163-1169.
65. Eisenhofer G, Bornstein SR. Surgery: risks of hemodynamic instability in pheochromocytoma. *Nat Rev Endocrinol*. 2010 Jun; 6(6):301-302.
66. Young WF, Kaplan NM, Kebebew E. Treatment of pheochromocytoma in adults. UpToDate. Waltham, MA: Wolters Kluwer Health; 2012. http://www.uptodate.com. Accessed 8 March 2012.
67. Claure RE, Drover DD, Haddow GR, Esquivel CO, Angst MS. Orthotopic liver transplantation for carcinoid tumour metastatic to the liver: anesthetic management. *Can J Anaesth*. 2000 Apr; 47(4):334-337.
68. Dierdorf SF. Carcinoid tumor and carcinoid syndrome. *Curr Opin Anaesthesiol*. 2003 Jun;16(3):343-347.
69. Goldfinger SE, Strosberg JR. Treatment of the carcinoid syndrome. UpToDate. Waltham, MA: Wolters Kluwer Health; 2012. http://www.uptodate.com. Accessed 8 March 2012.
70. Segal D, Holcberg G, Sapir O, Sheiner E, Mazor M, Katz M. Neurofibromatosis in pregnancy. Maternal and perinatal outcome. *Eur J Obstet Gynecol Reprod Biol*. 1999 May;84(1):59-61.
71. Richardson MG, Setty GK, Rawoof SA. Responses to nondepolarizing neuromuscular blockers and succinylcholine in von Recklinghausen neurofibromatosis. *Anesth Analg*. 1996 Feb; 82(2):382-385.
72. Hummel T, Anyane-Yeboa A, Mo J, Towbin A, Weiss B. Response of NF1-related plexiform neurofibroma to high-dose carboplatin. *Pediatr Blood Cancer*. 2011 Mar;56(3):488-490. Epub 2010 Nov 11.
73. Malav IC, Kothari SS. Renal artery stenosis due to neurofibromatosis. *Ann Pediatr Cardiol*. 2009 Jul;2(2):167-169.
74. Hersh JH; American Academy of Pediatrics Committee on Genetics. Health supervision for children with neurofibromatosis. *Pediatrics*. 2008 Mar;121(3):633-642.
75. Rasmussen SA, Yang Q, Friedman JM. Mortality in neurofibromatosis 1: an analysis using U.S. death certificates. *Am J Hum Genet*. 2001 May;68(5):1110-1118. Epub 2001 Mar 28.

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