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Spinal Surgery in Patients with Type-1 Neurofibromatosis: A Comprehensive Review

Cirurgia da coluna em pacientes com neurofibromatose do tipo 1: Uma revisão abrangente

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Abstract

Type-1 neurofibromatosis (NF1) is a neurocutaneous syndrome classically known as peripheral NF to distinguish it from type-2 NF (central NF). Its main characteristic is the high predisposition to the growth of multiple tumors, which specially arouses the interest of spinal surgeons due to the presence of spinal cord compression and spinal deformities.

Considering this, we have performed a comprehensive review, with illustrative cases of the main manifestations of NF1, focusing on the perspective of the spine surgeon. Articles were grouped according to the following subjects: diagnosis, skeletal complications, spinal deformity, and spinal tumors. For all of them, a detailed discussion on pearls for practice was presented.

The diagnosis of NF1 is based on the presence of at least two out of seven criteria. Cutaneous findings are very common in NF1, and the most usual tumor is cutaneous neurofibroma (NFB). Plexiform neurofibromas are also found and present a high risk of becoming malignant peripheral nerve sheath tumors (MPNSTs), reducing life expectancy. Astrocytomas, especially pilocytic astrocytomas, are the most common central nervous system tumor, including in the spinal cord. Surgery is necessary to resect as much as possible without adding new neurological deficits. Spinal deformities are also commonly found (in 30–70% of the cases), potentially associated with dystrophic changes, which may result in acute and rapid progression.

In the present review, we discuss specific characteristics found in this group of patients which are of paramount importance to properly manage this challenging disease.

Keywords

- neurofibromatosis
- spinal surgery
- pilocytic astrocytomas
- dystrophic
- deformity

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Resumo

A neurofibromatose do tipo 1 (NF1) é uma síndrome neurocutânea classicamente conhecida como NF periférica para distingui-la da NF do tipo 2 (ou NF central). Sua principal característica é a alta predisposição ao crescimento de múltiplos tumores, o que desperta especialmente a interesse dos cirurgiões de coluna devido à presença de compressão medular e deformidades.

Diante disso, realizamos uma revisão abrangente, com casos ilustrativos das principais manifestações da NF1, com foco na perspectiva do cirurgião de coluna.

Os artigos foram agrupados de acordo com os seguintes assuntos: diagnóstico, complicações esqueléticas, deformidade da coluna vertebral e tumores da coluna vertebral. Para todos esses assuntos, uma discussão detalhada sobre dicas para a prática foi apresentada. O diagnóstico de NF1 é baseado na presença de pelo menos dois dos sete critérios. Achados cutâneos são muito comuns na NF1, sendo o tumor mais comum o neurofibroma cutâneo (NFB). Neurofibromas plexiformes também são encontrados e apresentam alto risco de se tornarem tumores malignos da bainha do nervo periférico (MPNSTs), reduzindo a expectativa de vida. Astrocitomas, especialmente astrocitomas pilocíticos, são os tumores mais comuns no sistema nervoso central, inclusive na medula espinhal. A cirurgia é necessária para ressecar tanto quanto possível sem adicionar novos déficits neurológicos. As deformidades da coluna também são comumente encontrada (em até 30–70% dos casos), potencialmente associada a deformidades distróficas que podem resultar em progressão aguda e rápida.

No presente artigo, discutimos características específicas encontradas neste grupo de pacientes que são de suma importância para manejar adequadamente pacientes com esta doença desafiadora.

Palavras-chave

- neurofibromatose
- cirurgia da coluna vertebral
- pilocítico astrocitomas
- distrófico
- deformidade

Introduction

Neurocutaneous syndromes comprise many diseases that concurrently affect the skin, eyes, and central nervous system (CNS), potentially affecting other organs.[1] They are also known as *phakomatosis* (from the Greek *phacos*, meaning lens, and *phaos*, meaning light, that is "tumor of the lenses" due to retinal affectation in some patients). The most common entities are tuberous sclerosis (Boyrneville disease), von Hippel-Lindau disease, Sturge-Weber syndrome (Sturge-Weber-Dimitri syndrome or encephalotrigeminal angiomatosis), and the focus of the present study: neurofibromatosis (NF).[1]

In this context, NF consists in three distinct entities with different genetic inheritance: type-1 NF (NF1) – classically known as von Recklinghausen disease or peripheral NF; type-2 NF (NF 2) – formerly known as central NF, characterized by the presence of vestibular schwannomas; and schwannomatosis (SCH) – a rare entity with multiple schwannommas but without vestibular schwannomas.[2] The main characteristic of all NFs is the high predisposition to the growth of multiple tumors in the entire body.

In the current study, we present a comprehensive narrative review, with illustrative cases of the main manifestations of NF1, focusing on the perspective of the spine surgeon.

Materials and Methods

An electronic search on the Pubmed database was performed on October 8th, 2021 using the following keywords: *neurofibromatosis* + *spine* + *surgery*. The author evaluated all abstracts and grouped them with the aim of discussing the management and characteristics of spinal diseases in the context of NF1.

Clinical cases from the database of the authors' institution were presented to illustrate the technical challenges and strategies that may be used to treat these patients (approval form the institutional review board was obtained under number 17337313.7.0000.5404). A total of 481 articles were screened, and cross-referenced articles were used when necessary. Articles were grouped according to the following subjects: diagnosis, skeletal complications, spinal deformity, and spinal tumors. For all of them, a detailed discussion on pearls for practice was presented.

Results

Diagnosis of NF1

The inheritance pattern of NF is autosomal dominant in about 50% of the cases, and sporadic (*de novo* mutation) in the remaining cases – due to a mutation in the long arm of chromosome 17 (*ras protein*). There is no gender predilection.

The diagnosis of the multisystem disease syndrome of NF1 is characterized by at least two out of seven criteria in the absence of an alternate diagnosis (►**Table 1**).[3–6]

Cutaneous findings are much more common in NF1 than in NF2, but the latter has a higher incidence of CNS tumors, even though patients with NF1 may have optic nerve

Table 1 Diagnostic criteria for type-1 neurofibromatosis (NF1) and their estimated prevalence

Diagnostic criteria*	Estimated prevalence
Six or more café-au-lait spots or hyperpigmented macules (> 5 mm in prepubertal patients or > 15 mm in postpubertal patients)	95%
> 2 freckles (axillary or inguinal)	87%
≥ 2 typical neurofibromas or one plexiform neurofibroma	40–60% and 35% respectively
Optic nerve glioma	6%
≥ 2 iris hamartoma (also known as Lisch nodules)	78%
Sphenoid dysplasia or typical long-bone abnormalities	5%
First-degree relative with NF1 (parent, sibling, or offspring defined by the aforementioned criteria)	50%

Note: *The diagnosis requires the fulfillment of at least two of the diagnostic criteria.

gliomas, spinal cord tumors, and vascular abnormalities in the CNS. Life expectancy is shorter for patients with NF1 (about 8 years lower than that of the general population), especially due to malignant transformation of neurofibromas (NFBs) and plexiform NFBs into malignant peripheral nerve sheath tumors (MPNSTs).[7]

The phenotypical expression of NF1 patients varies greatly, and its natural evolution is unpredictable.[8] As a rule, the phenotypical presentation of the disease is more pronounced with aging, since many patients present more prominent cutaneous findings between the fourth and fifth decades of life. Despite that, by the age of 3 years, 99% of NF1 patients present café-au-lait spots.[8]

Skeletal Complications in NF1

Skeletal changes, as well as other phenotype characteristics, may vary from focal to generalized bone disorders.[9] Focal changes include spinal deformities, pseudoarthrosis of the tibia and forearm, chest-wall deformities etc. Generalized disorders are more common and may include severe bone malformations with dysplasia, osteoporosis, osteomalacia, shortness of stature and macrocephaly.[9]

Another commonly-found skeletal change are defects of the posterosuperior wall of the orbit (it is also a diagnosis criterion of NF1), intrathoracic meningocele, erosive defects of the bone from contiguous neurogenic tumors, anomalies of lumbar segmentation, spina bifida occulta, among others.[9]

Although NF1 is basically characterized by dysplasia of the neurectoderm, there is also mesoblastic dysplasia associated, which is responsible for the skeletal and soft-tissue changes.[9] These mesoblastic defects explain why some patients may present with "elephantoid masses of soft tissue" anywhere in the body.[9] These masses may also contain a hemangiomatous component, which generally involves a lower limb unilaterally or the head and neck.

Spinal Deformities

More than 20% of NF1 patients have some degree of spinal deformity,[10–12] which may be dystrophic or not, and is classified according to the presence of at least three dystrophic components. The most common dystrophic spinal changes are presented in ►**Table 2**. They are associated with more pronounced progression of spinal deformities and a more unfavorable outcome (from a skeletal as well as from a neurological perspective).

Thoracic and Lumbar Scoliosis and Kyphoscoliosis

The most common spinal deformity found in patients with NF1 is scoliosis. The reasons for this high prevalence may be mesodermal dysplasia, osteomalacia, bone erosion, and endocrine disturbances. Considering a general outpatient scoliosis clinics, about 2% of the patients had NF1, but up to 20% of the NF1 patients had scoliosis.[10–12] Non-dystrophic patients have curvatures similar to those with idiopathic scoliosis, with less severe deformities than those with dystrophic curvatures.

As aforementioned, deformity in NF1 can be dystrophic or non-dystrophic, and fortunately the latter is more commonly found.[13] Three or more of the dystrophic features presented in ►**Table 2** categorize patients as having dystrophic deformities. The management of non-dystrophic deformity is basically the same as the one provided to non-NF1 patients, using similar algorithms for surgical indications, such as surgical treatment for curves of more than 40°. On the other hand, dystrophic deformities are associated with progressive deterioration, extremely severe deformities, and clinical dysfunction.[12,14] Some patients may initially present a

Table 2 Diagnostic criteria for dystrophic deformity*

Vertebral scalloping (characterized by a concavity in the posterior vertebral body wall observed in spinal images on lateral projection)
Widening of the vertebral canal and neural foramina
Spindling of the transverse process
Spinal deformities – scoliosis, kyphosis, or kyphoscoliosis
Severe rotation of the apical vertebra in spinal scoliosis
Dural ectasia
Defective pedicles (sometimes precluding spinal fixation using screws due to their small diameter)
Rib penciling

Note: *The diagnosis is established in the presence of three or more components.

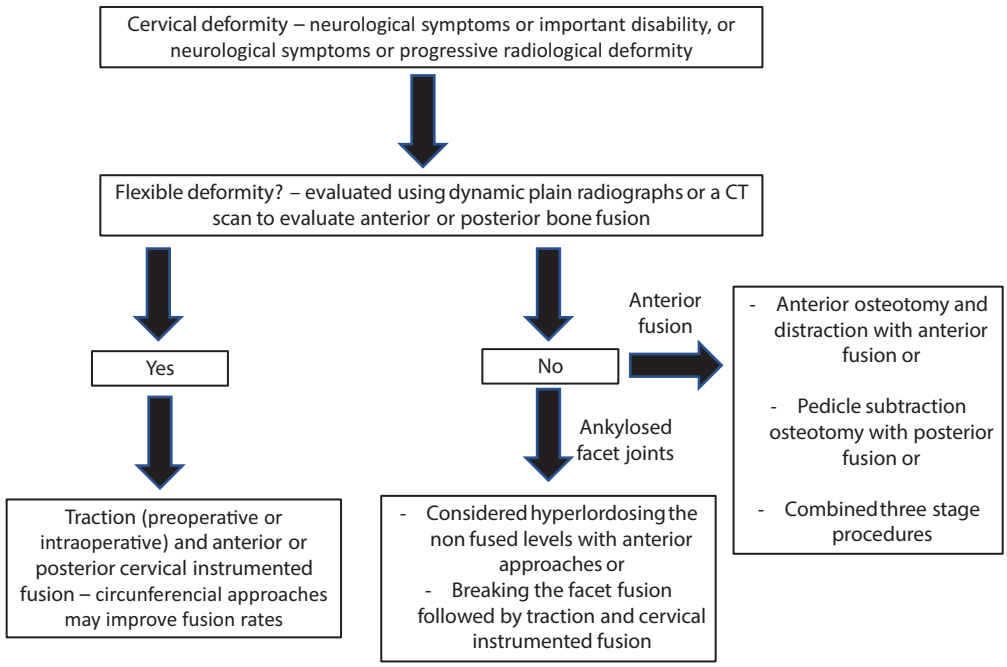

Fig. 1 Algorithm proposed to help in the management of cervical deformity. Adapted from Joaquim AF and Riew KD. Management of Cervical spine deformity after intradural tumor resection. Neurosurg Focus 2015;39(2):E13.

non-dystrophic deformity that can become dystrophic with aging.[15] Dystrophic deformities are associated with kyphosis, and they present a higher incidence of neurological deficits. In NF1, a magnetic resonance imaging (MRI) scan is recommended to all cases of spinal deformities since it is much more sensitive when it comes to detecting dystrophic changes. Some authors[16,17] have suggested that dystrophic curvatures should be surgically treated even if they present 20° to 40° due to their unfavorable and rapid evolution.

Challenges in dystrophic patients include poor bone quality, abnormal spinal anatomy, high severity of deformities, as well as difficulty in achieving fusion. Additionally, postlaminectomy deformities are more prominent in NF1 patients, especially those with dystrophic changes.

The most dramatic situation in NF1 is vertebral dislocation in highly-dystrophic kyphoscoliosis. This is a rare situation that may lead to neurological paraplegia and require complex procedures. In the spinal literature, some authors[18] have proposed the use of a halo-pelvic traction (HPT) apparatus – an external fixation system that provides a gradual correction (between one and two months) before the definitive surgical management – which is normally used between four and eight weeks before surgery. Halo-gravity traction (HGT) has also been proposed to improve curves preoperatively in cases of severe deformities, such as those with great evidence of the kyphotic element over the scoliotic curve with an acute angulation.[9] The rate of preoperative correction of the curve may be of about 40% with the preoperative use of HTP or HGT, decreasing the morbidity of the procedures and the need for more extensive osteotomies.

Cervical Kyphosis

Severe kyphosis is the most common cause of neurological deficits in NF1–in general, it is characterized by an acute anteroposterior angulation and deformed vertebral bodies that may be confused with congenital deformities. Cervical kyphosis may also be accompanied by a large neck NFB, which may increase the difficulty to treat these patients, as well as the morbidity of any eventual procedure.

Generally, some patients may need anteroposterior approaches for dystrophic cervical kyphosis, with higher potential for correction, even though only anterior or only posterior approaches may also be used.[19] Our algorithm to treat cervical kyphosis is presented in ►**Figure 1**[20] and an illustrative case is presented in ►**Figure 2**.

Most of the authors,[20] including us, have proposed that moderate correction is a reasonable and safer strategy in severe dystrophic cervical kyphosis.

The strategies described to treat severe cervical kyphosis include osteotomies followed by traction and definitive surgery; HGT is commonly reported[21] as a useful tool for severe cervical kyphosis or even severe kyphoscoliosis that should be employed preoperatively for four to six weeks to improve spinal alignment, decreasing the morbidity of the procedures.

Spinal tumors

Neurofibromas

The most common tumor found in NF1 patients are NFBs, followed by plexiform NFBs, MPNSTs, and glial tumors.[22] Contrary to NF2, the tumors are less frequently found in the intradural spinal compartment in NF1 (less than 10% of the cases), with most of them located laterally to the neuroforamina.[23]

The symptoms may include neuropathic pain, paresthesia, and even motor and sensory deficits due to spinal cord compression. Surgery is also considered for those with a

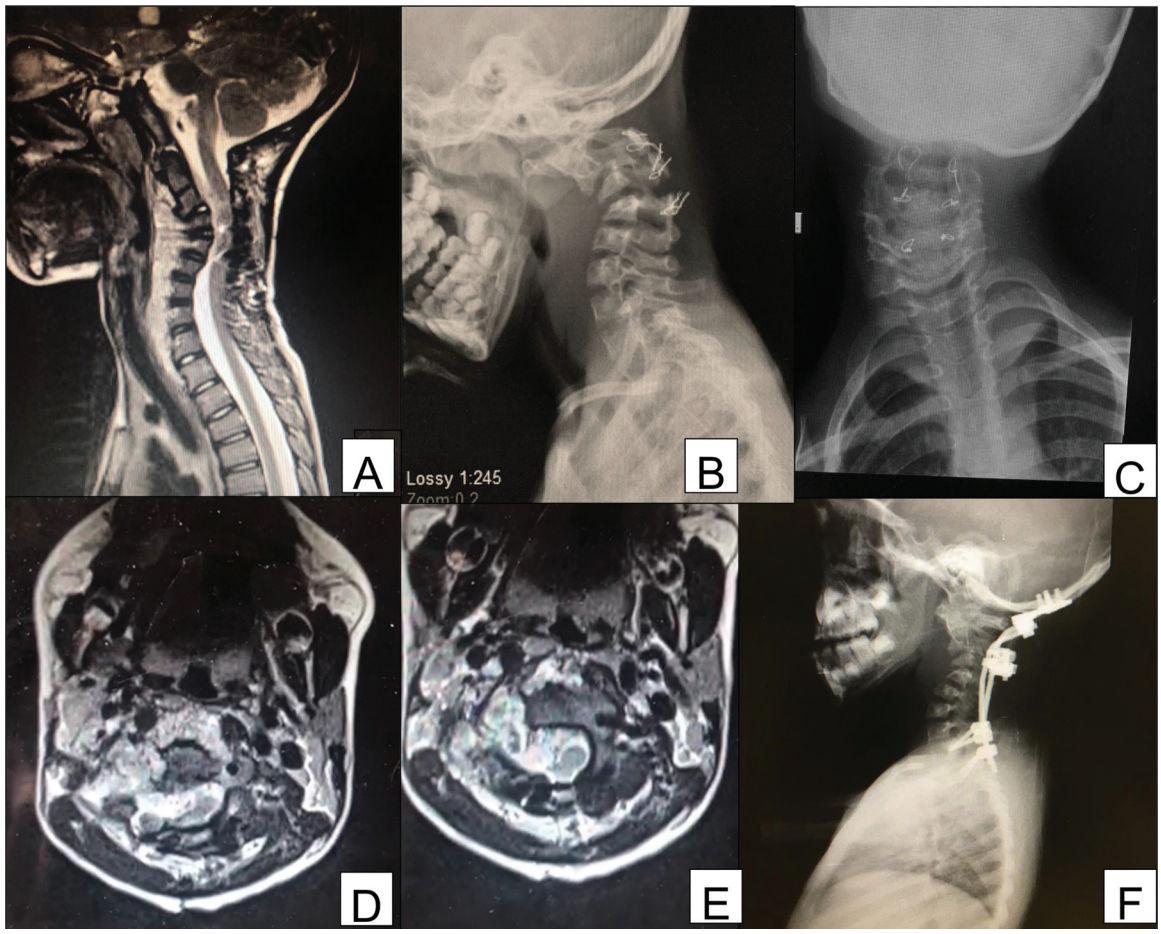

Fig. 2 A 6 year-old boy who underwent a previous C2-3-4 laminoplasty for resection of an intradural neurofibroma developed postoperative cervical kyphosis, with important pain and difficulty in swallowing, as shown in (**A**) the sagittal cervical magnetic resonance imaging (MRI) scan in T2-weighted sequence, and (**B**) in lateral and (**C**) anteroposterior plain cervical radiographs. Since the patient also had a giant anterior cervical neurofibroma, as shown in (**A**) and in (**D, E**) – axial T2-weighted sequence cervical MRI, the option of an anterior cervical surgery with tumor resection was refused by his parents due to the need of postoperative tracheostomy. We opted for preoperative traction using progressive adjustments of a halo vest for six weeks, followed by posterior occipito-cervico-thoracic fusion, because the lateral masses were too small and dysplastic for screw fixation. The patient presented persistent residual segmental kyphosis but with a good and acceptable head position after surgery, with significant improvement in symptoms.

suspicion of malignant transformation. Large dumbbell tumors, especially in the cervical spine, may require combined cervical approaches. The need for a combined or an isolated cervical approach depends on the extension of the NFB anteriorly or posteriorly, as well as the involvement of the vertebral artery. ►**Figure 3** presents an illustrative NFB found in a routine plain thoracic radiograph.

Taleb et al.[24] reported the results of 22 cases of cervical spine NFB operated on at their institution. The mean age at presentation was of 42.5 years, and most of the patients had progressive myelopathy. In total, 11 (50%) underwent complete tumor removal, and 10 were submitted to spinal instrumented fusion during the first procedure, 6 of them requiring an additional procedure. Overall, 8 out of the 12 patients who did not undergo instrumented fusion at the first surgery required a second procedure, 5 of which included instrumented fusion. Finally, four patients required a third procedure and instrumented fusion. Most of the patients required instrumented fusion at some point of the follow-up. One patient died in this series. The lesson learned is that decompressive procedures in the cervical spine in NF1 patients will ultimately cause some degree of deformity, even in adult patients.

Sometimes, NFBs are found bilaterally in two nerve roots at the same spinal level, resulting in significant cord compression. These typical lesions are known as "kissing neurofibromas" and symptomatic tumors (generally with progressive myelopathy in the cervical spine) are surgically treated to relieve cord compression (►**Figure 4**).[25] Cervical spine "kissing" tumors are more prone to require surgical treatment than lumbar tumors due to the presence of the spinal cord.[25]

Plexiform NFBs are present in about 30% to 50% of NF1 patients, and they may degenerate in about 10% of the cases to malignant transformation.[26] They are diffuse tumors that involve multiple nerve branches and trunks, potentially reaching very large dimensions. Radiologically, they generally present a hypointense signal in T1-weighted sequences, and hyperintense signal in T2-weighted sequences and short-tau inversion recovery (STIR), with central areas of

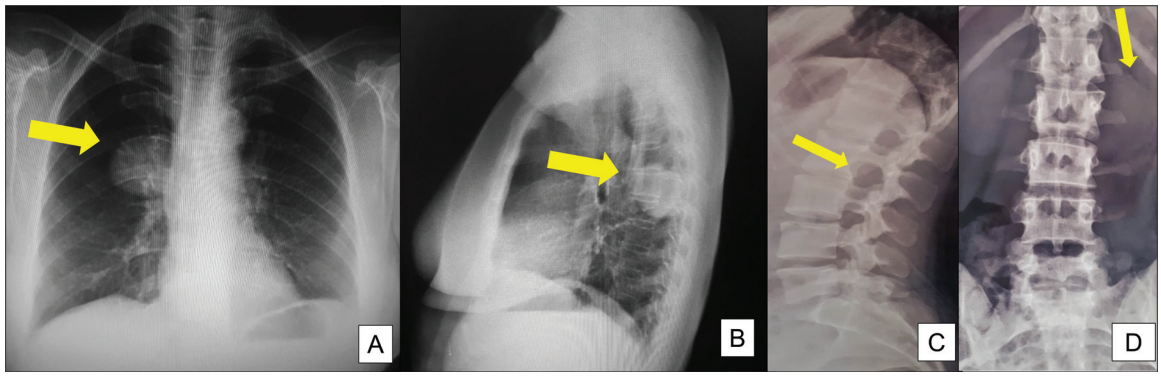

Fig. 3 Anteroposterior (**A**) and lateral (**B**) plain thoracic radiographs of an NF1 patient, showing a thoracic mass (yellow arrows). Another illustrative case – Lateral (C) and anteroposterior (D) plain lumbar radiographs of a patient complaining of lumbar pain, showing an enlargement of the neural foramen and pedicle remodeling (yellow arrow – C) as well as amass between the transverses process of the upper lumbar spine (yellow arrow – D).

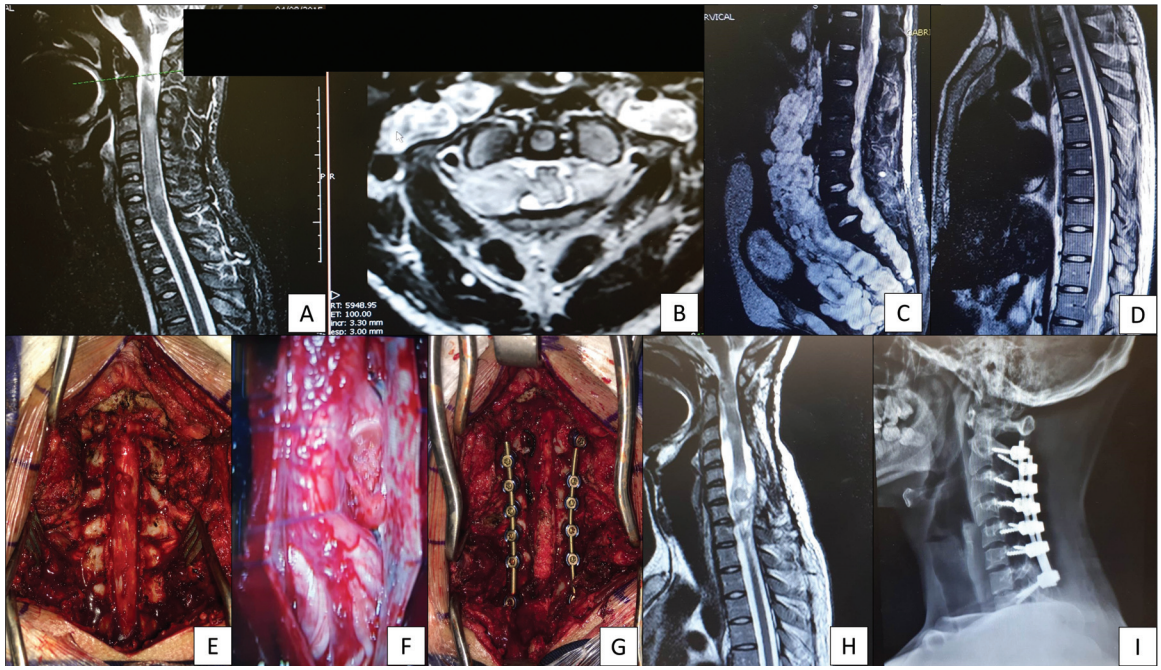

Fig. 4 Sagittal (**A**) and axial (**B**) cervical T2-weighted sequence MRI scans of an 18-year-old patient with multiple kissing neurofibromas and severe tetraparesis. He underwent a C2–C7 laminectomy with duroplasty for enlargement of the spinal canal with microsurgical partial resection of the multiple neurofibromas guided by neurophysiological monitoring (F). C2–T1 posterior instrumented fusion was performed to avoid postlaminectomy deformity. Postoperative sagittal T2-weighted sequence MRI showing good spinal cord decompression (**H**); final plain cervical lateral radiograph (**I**). The neurofibroma at T12 was also submitted to surgery, and the patient had great improvement in his neurological deficits.

low signal. The clinical symptoms may include mass effect, pain, bone changes/deformity, intratumoral bleeding, neural compression symptoms, and malignant transformation.

Surgery for non-malignant NFB is generally indicated for symptomatic lesions with progressive deficits, since it is not feasible to remove all asymptomatic tumors and most of the patients only undergo partial tumor removal due to the neurological morbidity of an aggressive surgery.[22]

Anecdotal case reports have suggested that the mitogen-activated protein kinase (MEK) inhibitor may cause shrinkage of plexiform NFBs. Vaassen et al.[27] reported the case of an 11 year-old NF1 patient who had a reduction of about 22% of a large plexiform NFB after 6 months of therapy. Further studies are necessary to evaluate the impact of the use of MEK inhibitor in tumor control.

In the case of suspicious of histological malignant transformation, such as large tumors or rapid tumor growth with or without persistent pain, fluorodeoxyglucose (FDG)-positron emission tomography (PET) is recommended in conjunction with MRI to perform an early diagnosis.[28] Generally, MPNSTs present high fluorodeoxyglucose (FDG) uptake and large dimensions (those larger than 6 cm are very suspicious).[29] Commonly found in NF1 patients in the second and third decades of life, MPNSTs are very aggressive lesions. They are the most common malignant tumor in NF1, with an impact on overall survival. The best treatment modality is

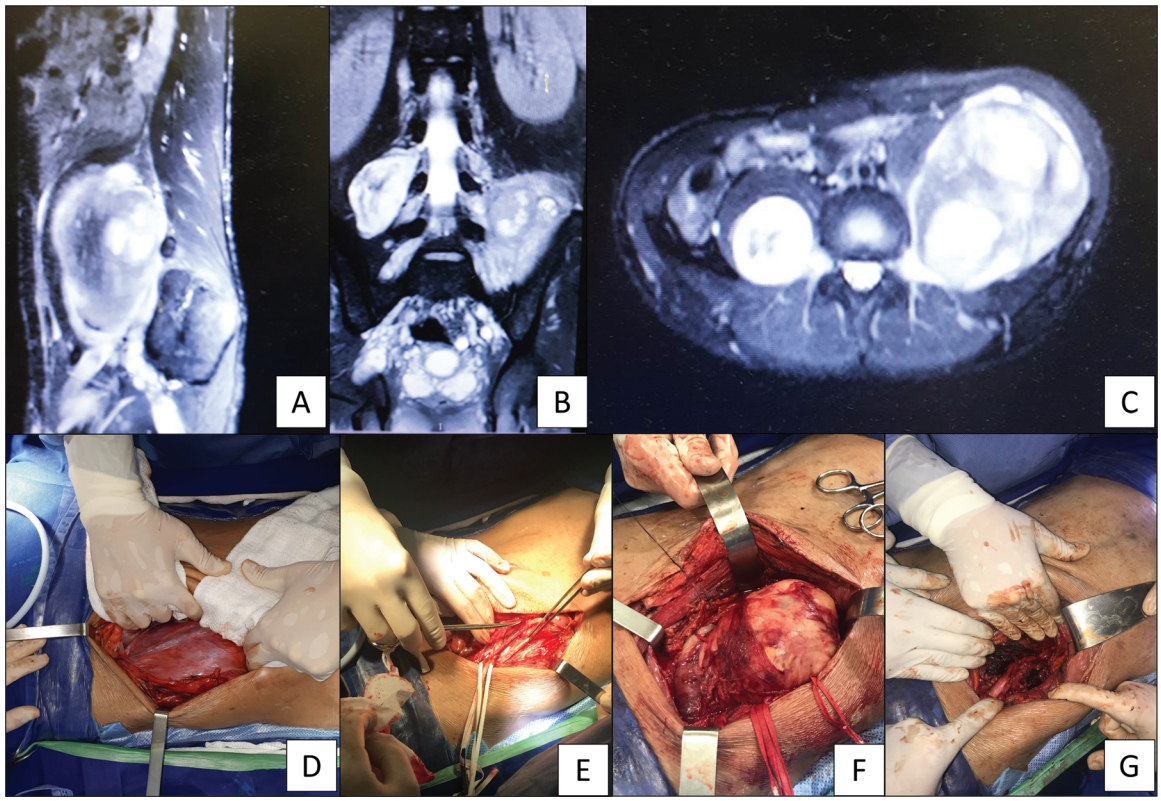

Fig. 5 An 18-year-old NF1 patient who complained of an abdominal mass and constipation. He had a giant left retroperitoneal neurofibroma, as shown in the sagittal (**A**), coronal (**B**), and axial (**C**) abdominal CT scans. A left retroperitoneal approach was performed (**D**), and we identified and isolated the multiple nerves of the lumbar sacral plexus (**E**) through en bloc resection of the mass (**F**). Total resection of the malignant peripheral nerve sheath tumor was achieved (**G**).

aggressive surgical resection. Incomplete resection may be treated with adjuvant chemotherapy with doxorubicin and ifosfamide. Radiotherapy is controversial, and its role is still under debate. ►**Figure 5** presents an illustrative case of MPNST that was surgically treated.

Finally, as aforementioned, postoperative instability is much more common in NF1 patients submitted to spinal laminectomy for intracanal tumor removal due to tumor-related changes, bone reabsorption, bone dystrophia, and osteoporosis. Therefore, closer radiological and clinical follow-ups for the early diagnosis of deformities recommended in cases in which it was not clear at the time of the surgery for tumor resection if instrumented fusion would be beneficial. Dural ectasia and lateral meningoceles, the soft components of NF1, may lead to weakness of the spine and favor deformities.[30]

Intramedullary Tumors

Intramedullary tumors are less common in NF1 than in NF2 patients.

The most common intracranial tumors in NF1 are pilocytic astrocytomas that preferentially involve the optic nerves and chiasm. The same is true for intramedullary spinal cord tumors (IMSCTs). Kushel' et al.[31] have reported that, in a large series of 541 patients with IMSCT, 7 patients had NF1–5 of whom with pilocytic astrocytoma, 1 with an anaplastic astrocytoma (the only adult patient with NF1, aged 51 years), and 1 with a thoracic ependymoma –, mostly children and adolescents. Only for the purpose of comparison, considering the 15 patients with NF2, 12 of them had ependymoma, 2 had pilocytic astrocytoma, and 1 presented a fibrillary astrocytoma. Their findings[31] suggest a strong link between astrocytoma and NF1 in children and adolescents, and ependymomas and NF2.

The generally accepted indications for surgery are symptomatic or asymptomatic tumors with progressive radiological findings.

Though rare, other histologies have been reported in NF1, such as gangliogliomas, primitive neuroectodermal tumors (PNETs), anaplastic astrocytomas, and even neurinomas have been reported anecdotally.[32–34]

The surgical treatment for IMSCT consists in resection of as much tumor as possible guided by neurophysiological monitoring, to avoid further neurological deficits. Ependymomas and some pilocytic astrocytomas may be totally resected in some cases of focal and circumscribed tumors. For malignant astrocytomas, adjuvant chemotherapy and radiotherapy may also be considered, despite a very unfavorable outcome.

Chalenges in Spinal Surgery in NF1

The very thin laminae of some patients, due to tumor erosion or dural ectasia, may preclude the use of hooks, wires, and screws. Therefore, a careful examination of bone anatomy through computed tomography (CT) scans is advisable before the development of a surgical plan.

Cerebrospinal fluid leak due to the very thin laminae is also a potential complication that may be decreased with diligent dissection and external lumbar drains when necessary.

Extensive bleeding from venous lakes and from blood vessels in the cancellous bone requires the use of hemostatic agents and proper anesthetic support.

Patients with NF1 frequently need to consult with a spinal surgeon and close clinical and radiological follow-ups. Understanding the nuances of the diseases, as well as the variability in presentations, is of paramount importance to properly manage these patients and decrease the suffering caused by this morbid syndrome.

Conflict of Interests

The author has no conflict of interests to declare.

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