Child's Nervous System (2019) 35:2289–2297
https://doi.org/10.1007/s00381-019-04306-w

ORIGINAL ARTICLE

Pediatric peripheral nerve tumors: clinical and surgical aspects

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Received: 3 July 2019 / Accepted: 10 July 2019 / Published online: 25 July 2019

Abstract

Purpose Pediatric peripheral nerve tumors (PNTs) are rare. Most are related to neurofibromatosis type 1 (NF1) with the potential for malignancy. An ongoing debate occurs about the best approach to such patients. This study describes a cohort of pediatric patients with PNTs and discusses clinical characteristics and surgical treatment.

Methods We retrospectively reviewed the charts of seven pediatric patients with eight PNTs surgically treated from 2007 to 2018. Information concerning patient demographics, clinical presentation, PNTs characteristics, treatment choice, and outcome were recorded.

Results All children presented with intense pain and a palpable mass. Three of the eight tumors were associated with a neurological deficit. Among the four patients with NF1, two had a neurofibroma and two a malignant peripheral nerve sheath tumor (MPNST). Histologically, three of the lesions were a benign peripheral nerve sheath tumor (BPNST), three a MPNST, and one each a desmoid tumor and Ewing's sarcoma. Two of the eight tumors underwent partial tumor excision and six gross total excisions.

Conclusions Intense pain at rest, day, and/or night, preventing normal activities; a palpable, hard, immobile mass; an intense Tinel's sign related to the lump; clinical evidence of NF1; and high-speed growth of a tumor in the trajectory of the nerve or plexus should alert the clinician to the potential for malignancy. Preoperative biopsy is not indicated when clinical and imaging findings suggest a benign tumor. The surgical management of PNTs must be to achieve total resection, including wide margins with malignant tumors, though this is not always possible.

Keywords Neurofibromatosis type 1 · Neurofibroma · Desmoid tumor · Pediatric malignant tumor

Introduction

Peripheral nerve tumors (PNTs), which usually affect adults, can also be found in children. They can be either neurogenic (most common) or non-neurogenic [1]. Peripheral nerve sheath tumors (PNST) are relatively rare, especially in the young [2–4]. They can be benign or malignant, the majority presenting as benign masses (schwannoma or neurofibroma) [5, 6].

Patients may present classical signs and symptoms, which include a lump in the trajectory of a peripheral nerve or brachial plexus, sensory deficits, muscular weakness, autonomic nerve malfunction, and pain [7, 8]. Previous studies suggest that a palpable/visible mass, nerve palsy, and pain are more common in malignant lesions than benign [8]. However, a large number of PNST do not display any symptoms, appearing as a "silent" lump that can, eventually, become visible or palpable [9]. For this reason, suspicion of such tumors can be delayed and the disease can be advanced by the time a patient is referred to a specialized center. Besides clinical evaluation, magnetic resonance imaging (MRI) is the method of choice for the initial investigation and treatment planning [10–13].

In children, PNST are chiefly related to neurofibromatosis type 1 (NF1), an autosomal dominant syndrome affecting the nervous system and skin [6, 14, 15]. Such patients have an increased risk of

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developing neurofibromas that involve multiple branches, roots, and plexi [2, 11, 14, 16]. The odds of malignant transformation and metastasis also increases with NF1, sometimes demanding immediate treatment [12, 15, 17, 18].

In this paper, we report a series of eight tumors in seven children, with and without NF1, which underwent surgical excision. One case has been described previously [19]. The aims of this paper are to describe clinical characteristics of PNTs in children and to discuss surgical treatment and outcomes.

Methods

This is a retrospective study of eight PNTs in seven pediatric patients treated within the Division of Neurosurgery at Gaffrée e Guinle University Hospital of Federal University of Rio de Janeiro State (UNIRIO), between January 2007 and December 2018. The mean age of the patients at the time of surgery was 11.6 years (range 3–18), with five female patients. Clinical data retrieved from medical records included the patient's age, gender, neurologic symptoms and signs (Table 1), clinical stigmata of NF1, location of the tumor, MRI findings, surgical data, postoperative results, and complications. NF1 was diagnosed in three patients, with one patient having two tumors. Each NF1 patient underwent genetic testing. Four patients had no NF1, each with one lesion.

Clinical evaluation consisted of a complete neurological examination, with the patient's motor deficits rated using the Medical Research Council scale [20] and pain rated on a visual analogue scale (VAS) [21].

Surgical management for benign PNTs was performed with gross total lesion resection in most cases, while the surgical approach for malignant PNTs was to attempt gross total resection. Intraoperative electrical nerve stimulation was employed during tumor dissection to localize functional and non-functional areas over the tumor surface, helping with tumor excision.

Follow-up consisted of clinical reevaluation every month for the first 6 months after surgery and every 3 months thereafter for benign tumors. For malignant tumors, patients were seen in the outpatient clinic every month for 12 months and referred to both pediatric oncology and medical genetics.

Results

All patients presented with intense pain and a palpable mass. Three patients had a neurological deficit, that progressively worsened: two of them had a brachial plexus upper trunk (BPUT) motor deficit (M2) (cases 1 and 2), while one (case 7) exhibited a tibial branch of the sciatic nerve (SN) deficit (M3). Three patients underwent electroneuromyography (ENMG) (cases 3, 4, and 6), with normal results, and all patients underwent MRI.

The excision was partial in two cases and gross total in six. Two patients had surgical complications: case 1 developed a chylothorax, treated with a drain for 10 days with good resolution; case 2 had persistent dysphagia. Preoperative pain improved in all patients (mean postoperative VAS = 0.43/10). All three children with previous neurological deficits improved after surgery to M4. Histology revealed six PNST, one desmoid tumor, and one Ewing's sarcoma. Three PNST were neurofibromas, while the other three were MPNST. In NF1 patients, two tumors were benign neurofibromas, while two were MPNST.

The 11-year-old female (case 1) diagnosed with NF1 presented with a huge supra/infraclavicular mass of 1-year duration, causing BPUT motor deficit. MRI showed a mass in the BPUT invading the axillary and thoracic regions. Resection was gross total. Histopathological diagnosis was MPNST. She was referred to Pediatric Oncology and subsequentially received chemotherapy and radiotherapy. After 6 months of follow-up, her motor deficit had improved to M4 and

Table 1 Individualized data on patient age, gender, related NF1, and clinical features

Patient	Sex	NF1	Age	Clinical presentation
1	Female	Yes	7	Pain* (VAS = 9), stiff mass, TS present in the right brachial plexus, BPUT motor deficit (M2)
2	Male	Yes	3	Pain* (VAS = 8), TS present in the right brachial plexus, BPUT motor deficit (M2)
			11	Pain* (VAS = 9), stiff mass, TS present in the left cervical plexus
3	Male	Yes	12	Pain* (VAS = 7), TS present in the left SN trajectory
4	Female	No	12	Pain* (VAS = 7), TS present in the right SN trajectory
5	Male	No	14	Pain* (VAS = 9), stiff, mass, TS present in the right SN trajectory
6	Female	No	16	Pain* (VAS = 9), stiff mass, TS present in the right femoral nerve trajectory
7	Female	No	18	Pain* (VAS = 8), TS present in the right SN trajectory; tibial branch of the sciatic nerve motor deficit (M3)

*Pain prevented normal activities of the child and was present at rest and during the night

TS Tinel's sign, *BPUT* brachial plexus upper trunk, *SN* sciatic nerve

her pain had decreased. At 2-year follow-up, she reported no pain and remained tumor free.

Over 4 months, a 3-year-old male with NF1 (case 2) developed an intense painful right supraclavicular lump that prevented the child from sleeping or eating. Simultaneously, a BPUT motor deficit was observed. MRI revealed a heterogenous mass compromising the right BPUT and compressing the trachea and esophagus. One month before surgery, there was worsening of respiratory function, including dyspneic episodes, due to deflection of the trachea by the tumor. Gross total resection of the mass was possible (Fig. 1). The histopathological diagnosis was neurofibroma. Postoperatively, the child's pain resolved and motor function improved (M4). Nine years later, a rapidly growing posterior cervical mass appeared on the left. Gross total excision of the tumor was possible, after which, a final diagnosis of cervical plexus MPNST was made (Fig. 2). The Pediatric Oncology service initiated chemotherapy and radiotherapy. Nevertheless, after 6 months, the patient died with metastases in both lungs.

The SN was affected in the next two cases: a 12-year-old boy, diagnosed with NF1 (case 3) and a 12-year-old girl (case 4). MRI displayed huge heterogenous masses in the SN without invasion of the surround tissue. In case 4, gross total resection was possible; however, only partial excision was achieved (> 90%) in case 3, since the functional fascicles were difficult to separate from non-functional fascicles. A neurofibroma was diagnosed in both cases. Both patients' courses remained symptom-free through 5 years of follow-up, with no adjuvant treatment necessary.

Case 5 was another tumor involving the SN, on the right side. MRI suggested that the mass would be a benign neurogenic tumor. After exposure, the lesion was found to be highly heterogeneous (Fig. 3). An intra-operative biopsy was performed, which was inconclusive. A partial resection was done, after which, a final diagnosis of Ewing's sarcoma was made. Afterwards, the patient was referred to Oncology without neurological deficits or pain. Chemotherapy and radiotherapy were initiated and 5-year follow-up revealed no evidence of relapse.

Throughout 6 months, a huge and painful tumor affecting the femoral nerve developed in a 16-year-old girl without NF1 (Case 6). Incisional biopsy was performed at another institution, which was inconclusive. MRI (Fig. 4) revealed a heterogenous mass affecting the right femoral nerve. At surgery, it was possible to achieve gross total resection of the tumor, and biopsies showed no invasion of nearby structures. The histopathological diagnosis was a MPNST. No chemotherapy or radiotherapy was deemed indicated by Oncology. Unfortunately, however, 1 year later, the tumor recurred in the same place and there were metastases in both lungs. The patient is currently receiving adjuvant therapy.

The last case (case 7) involved an 18-year-old girl without NF1, who had a 3-year previous history of a mass in the dorsal right thigh. She was seen by another service and underwent a needle biopsy that revealed a desmoid tumor. At that time, a decision was made merely to observe the tumor over time. The tumor continued to grow. Embolization of the tumor and radiotherapy were tried but failed to prevent the lesion from progressively growing, resulting in SN deficits and invasion of the gluteus region. MRI of the gluteus region and thigh demonstrated a heterogenous mass affecting the right SN. The patient was sent to our division for tumor resection (Fig. 5). No attempt was made to resect the deep proximal gluteal mass, because at that time, it was asymptomatic. There was improvement on both the patient's pain and motor deficit. The tumor in the gluteus area has remained stable.

Table 2 summarizes the patients' diagnostic and surgical management.

Discussion

Neurogenic and non-neurogenic PNTs are rarely found in children. However, they constitute an important category, since they are frequently associated with genetic syndromes [22–24]. BPNST can be precursors of MPNST [4, 14], especially in NF1 patients. The prevalence of such tumors may increase in the setting of NF1 [14, 15, 25]. Here, we report a series of eight symptomatic PNTs in seven children, some of them with NF1. One case was described previously [19].

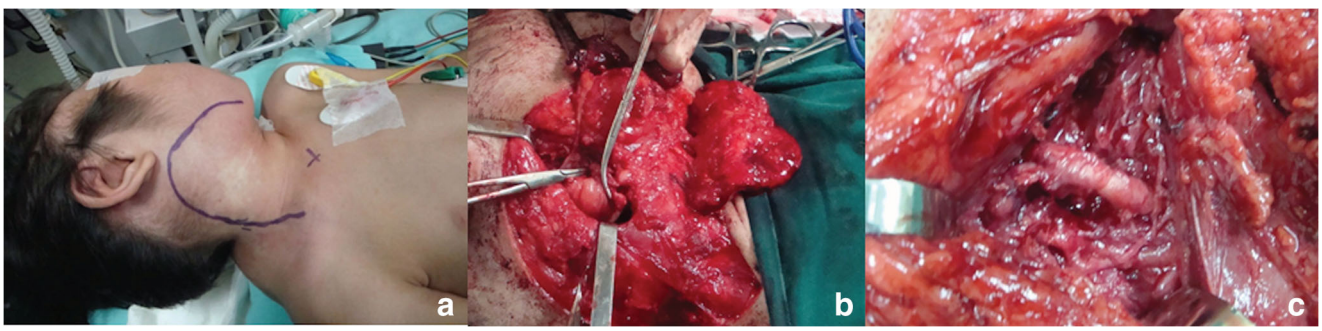

Fig. 1 **a** Surgical position of a NF1 patient with a right brachial plexus tumor. **b** Tumor being resected from the superior trunk of brachial plexus. **c** Region after surgical excision of the mass

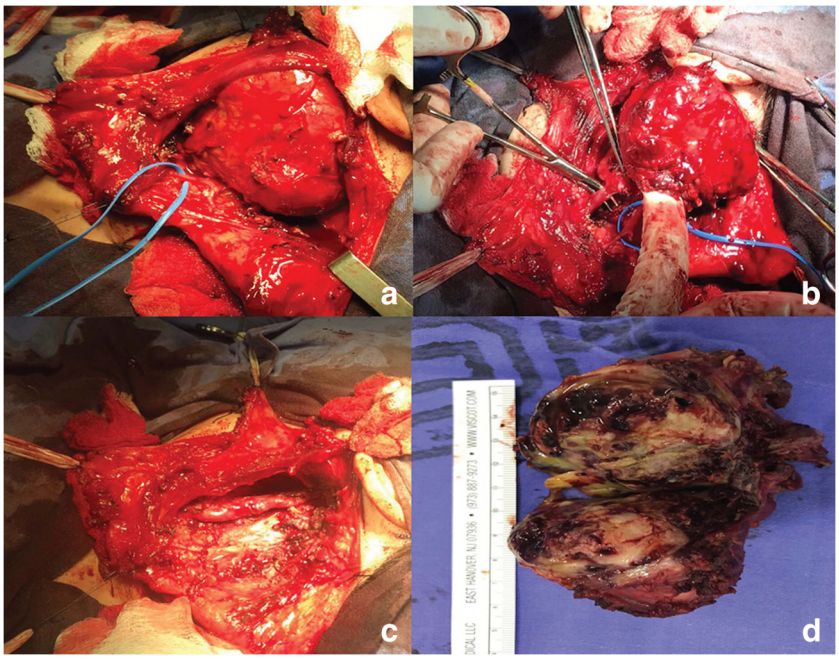

Fig. 2 Same patient of Fig. 1 9 years later. **a**, **b** Huge mass affecting left cervical plexus. **c** Region after resection. **d** Anatomopathological specimen

Three presented as BPNSTs (neurofibroma), three as a MPNST, one as a desmoid tumor, and one as Ewing's sarcoma. BPNSTs are by far the most common peripheral nerve tumor described in the literature, accounting for 81 to 90% of lesions [2, 3, 26]. Interestingly, DeCou et al. found only 22% of their PNTs to be benign in a pediatric series of 36 patients, which may be due to the small number of cases and strict patient-selection criteria [17].

On clinical presentation, intense pain, at rest and nocturnally; a tumor that prevents normal activities of the child; a stiff mass, sometimes rapidly growing; and a positive Tinel's sign were the main symptoms and signs in our cases. According to the literature, swelling, pain, and neurological deficits are considered major indicators for seeking medical advice [8, 12–17]. Three of our patients had a neurological motor deficit. Other clinical manifestations can also occur depending on the tumor site. The onset and severity of any symptoms must be highlighted, since they can play an important role in predicting malignancy [6, 8, 10, 27].

NF1 patients comprised three of our patients, which is in agreement with claims that such patients are more prone to develop PNST, especially neurofibromas and plexiform neurofibromas [2, 5, 6, 15, 16]. Valeyrie-Allanore et al. identified a PNT incidence of 16–40% in NF1 patients [15]. In a cohort study of NF1 patients, it was reported that symptomatic plexiform neurofibromas occurred in 37% of the children under 11.5 years old, in 55% of the adolescents above 11.5 years old, and in 69% of the adults [14]. This may indicate that a large number of these tumors can occur at a young age [14]. NF1 is associated with a global increase in the risk of developing benign and malignant tumors, as well as higher morbidity and mortality in both children and adults [7, 28, 29].

The initial diagnosis of PNTs necessitates thorough clinical and complementary exams, like ENMG and MRI [6, 10–13]. Of our patients, three had electrophysiological studies, all the results normal, while MRI was performed in all patients.

The preoperative biopsy of lesions with benign clinical and imaging features is controversial, since it can lead to

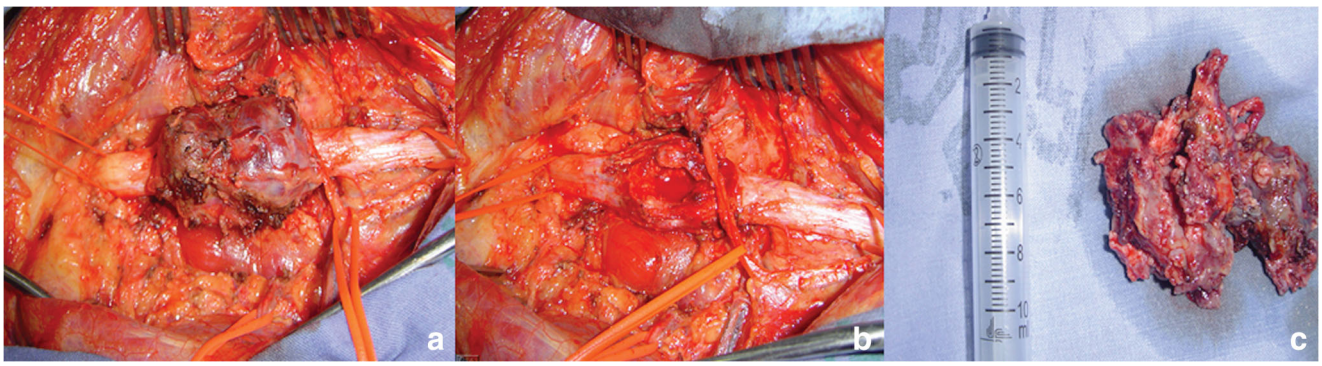

Fig. 3 **a** Tumor in right SN exposed. **b** Region after tumor resection. **c** Anatomopathological specimen

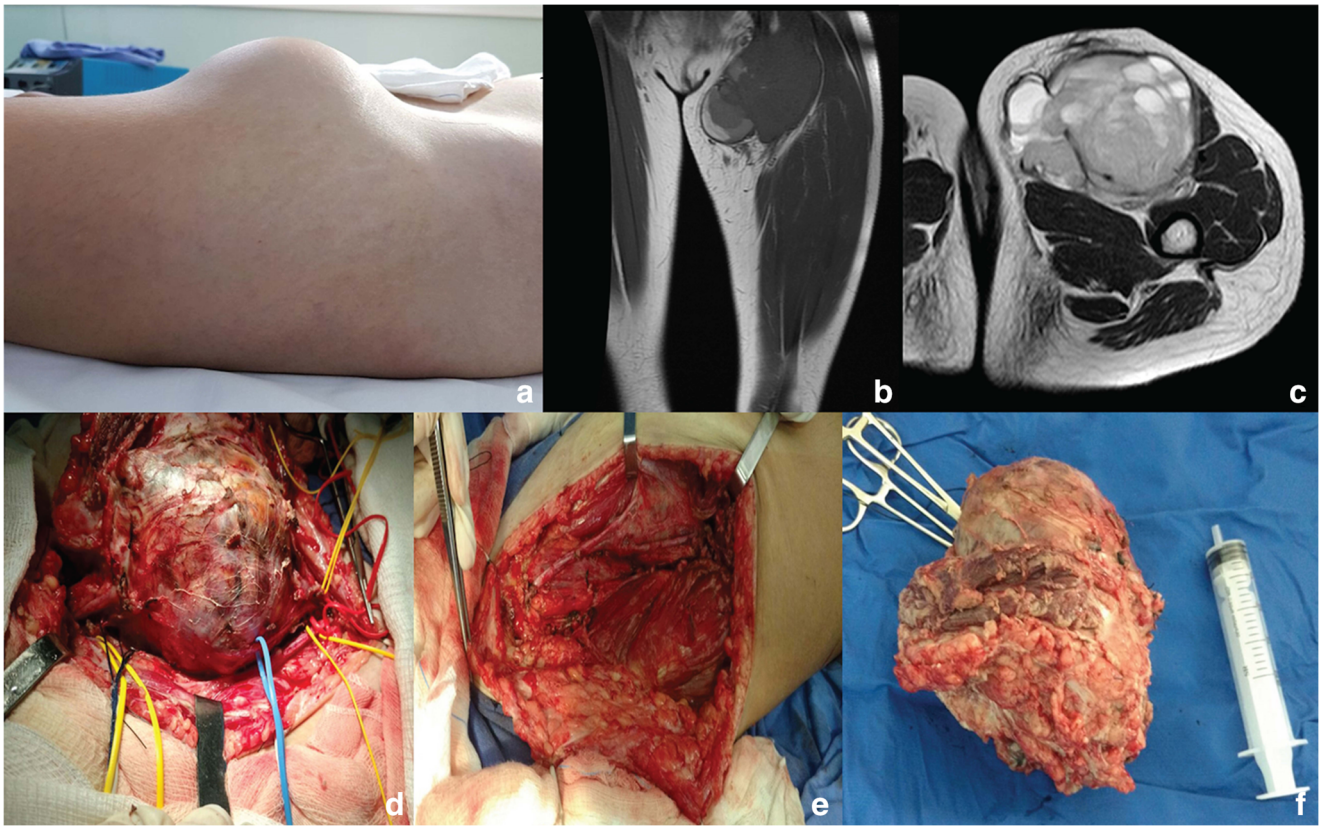

Fig. 4 **a** Huge lump on the anteromedial aspect of the right thigh. **b** Coronal T1-weighted MRI. **c** Axial T1-weighted post-gadolinium contrast showing the tumor. **d** Tumor exposed. **e** Region after excision femoral nerve and its branches free of tumor. **f** Anatomopathological specimen

inconclusive or inaccurate results, the onset or worsening of pain, neurological deficits, and other complications that may hamper future surgical excision and outcomes [30, 31]. Rodriguez et al. reinforce the challenge of making histopathological diagnoses, since hybrid benign nerve sheath tumors exhibit morphological and immunophenotypic features that indicate co-existing, distinct tumors, like neurofibroma and schwannoma [32]. We do not perform preoperative biopsies in cases that seem clinically and by imaging benign. However, certain clinical characteristics suggests a more aggressive course of management. Such characteristics include rapidly intensifying pain, at night and rest; pain that prohibits others from even touching or cleaning the child; the new onset of any sensory and/or motor deficit; rapid enlargement of a lump or known PNST; and a hard consistency. On MRI, characteristics that suggest malignancy are an irregularly or round mass usually larger than 5 cm, perilesional edema, necrosis/cystic change or hemorrhage, T1 heterogeneity, heterogeneous

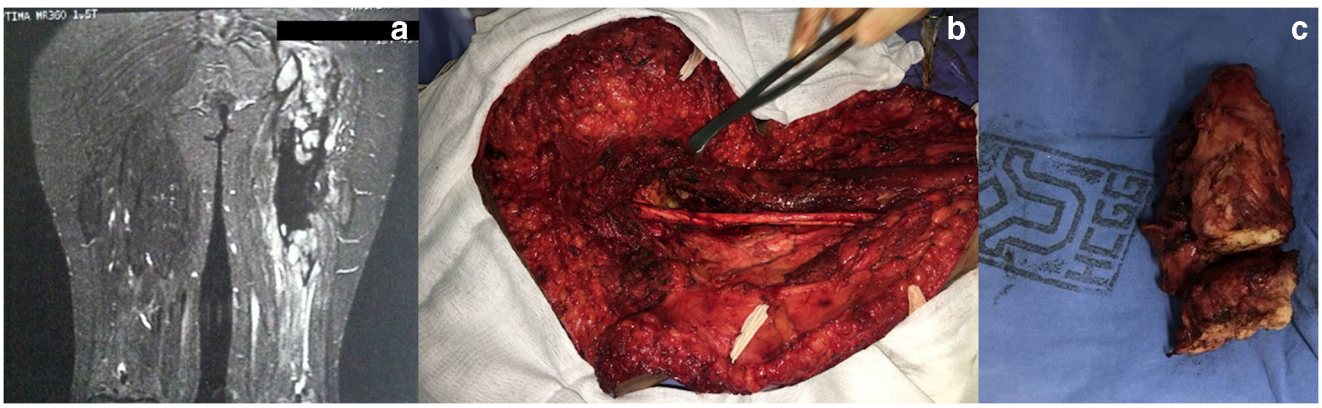

Fig. 5 **a** Right gluteus region and thigh STIR MRI showing mass affecting the SN. **b** Region after surgical excision: it is possible to observe the SN and its division free of tumor. **c** Anatomopathological specimen

Table 2 Tumor locations and outcomes

Patient	Location	Treatment	Histology	VAS pain after surgery	Outcome
1	Right brachial plexus	Gross total excision	MPNST	1	Pain decreased and motor deficit improved (M4)
2	Right brachial plexus	Gross total excision	Neurofibroma	0	Improved motor function (M4) and resolution of pain
	Left cervical plexus	Gross total excision	MPNST	1	Lung metastases. Died after chemo and radiotherapy treatment
3	Left SN in the proximal thigh	Partial excision	Neurofibroma	0	No clinical impairment; resolution of pain
4	Right SN	Gross total excision	Neurofibroma	0	No clinical impairment; resolution of pain
5	Right SN	Partial excision	Ewing sarcoma	1	No clinical impairment; pain decreased
6	Right femoral nerve	Gross total excision	MPNST	0	No clinical impairment and resolution of pain. Tumor recurrence and lung metastases identified 1 year later.
7	Right SN	Gross total excision of the SN component of the tumor	Desmoid tumor	0	Improved motor deficit (M4) and resolution of the pain

SN sciatic nerve

enhancement, a location deeper than fascial plans, and the invasion of nearby tissues; in such patients, a preoperative biopsy must be considered [8, 10]. In our cases, due to severe pain and compression of adjacent structures, we promptly decided for radical surgical excision before any other invasive procedure. However, in two patients (cases 6 and 7), a preoperative biopsy was performed elsewhere; results were inconclusive and diagnostic of a desmoid tumor, respectively.

Malignant peripheral nerve sheath tumors (MPNST) are rare aggressive tumors before 20 years, accounting for just 10–20% of PNTs [7, 17, 27, 33, 34]. This said, Takaeda et al. showed that neurogenic tumors have malignant presentation in 5.8% of adults, but 41.7% of children, indicating a tendency towards higher-grade tumors in youths [35]. Such masses usually arise from nerve trunks, especially the brachial plexus, SN, sacral plexus, and paraspinal nerve [4] Our series included three MPNST cases, all of which exhibited greater progression than our BPNST.

The association between PNST in NF1 patients and the risk of MPNST is well established in the literature [6, 12, 15, 18, 36, 37]. The lifetime risk of developing a MPNST ranges from 8 to 13% with NF1-linked plexiform neurofibromas [15, 18, 37]. Other investigators have identified other strengths of association between MPNST and NF1 [15, 17, 29]. Including adults, MPNST appears in 2–5% of NF1 patients, but in only 0.001% of the general population without NF1 [6, 25]. What this indicates is that it is crucial to evaluate patients with NF1 and PNTs thoroughly, to identify any signs or symptoms that might suggest malignancy [6, 10, 27].

Ewing's sarcoma is a highly malignant and aggressive tumor, characterized by pathognomonic FET-ETS gene fusions, but it is extremely rare in peripheral nerves [38]. Treatment strategies include multimodal therapy, where surgical resection, followed by chemotherapy and/or not radiotherapy is recommended, improving long-term survival [39–41]. In our case, partial excision of the lesion was possible, with preservation of the SN, after which, the patient was referred to the Pediatric Oncology service for adjuvant treatment. Follow-up over 5 years revealed no relapses.

Tumor resectability depends upon a combination of tumor location, size, consistency, degree of tissue invasion, and potential neurological consequences after radical resection. The most common sites in the pediatric population are extremities (40%), which favors resection due to generally easier access to the lesion [7, 25]. We reported two BPUT cases (one MPNST and one neurofibroma), four cases involving the SN (two neurofibromas, one desmoid tumor, and one Ewing sarcoma), one case involving the cervical plexus (MPNST), and one case involving the femoral nerve (MPNST). Basically, the surgical approach begins with full microsurgical exposure of the tumor, followed by electrical stimulation of the nerve surface to delimitate functioning fascicles to identify any electrically silent area to serve as the point of initial dissection. Gross tumor excision with tumor-free margins is the major objective, since it enhances overall survival and achieves total or partial resolution of pain in 75–85% of patients [2, 4, 14, 25, 42–44]. However, commenting on their series of eleven patients, An

et al. stated that there was no difference in the overall survival rate in treated patients with and without NF1 [45]. We achieved gross total resection of two neurofibromas, three MPNST, and one desmoid tumor, although some of these resections were difficult and it was necessary to perform a piece-meal resection technique. Meanwhile, only partial resection was possible for one NF and one Ewing's sarcoma, due both to the lesion's hard consistency and viable fascicles inside the lesion.

The postoperative prognosis for BPNST is usually favorable, with good outcomes achieved on follow-up. Among malignant lesions, the most important determinant of survival is gross tumor resection with tumor-free margins [27]. DeCou et al. found significant differences in 2-year survival between patients in whom total resection of the tumor was possible (79%) and those with unresectable tumors (22%) [17]. Prada et al. identified a 10-year recurrence rate of 28.8% in patients who underwent subtotal resection versus 54.9% with partial resection [44].

Relative to BPNST, MPSNT have a much poorer prognosis and higher recurrence rate, ranging from 4 to 50% in adult and pediatric populations, the results depending on the amount of tumor resected during surgery [25, 46]. Other prognostic indicators of poor outcome are a central location, large tumor size, presence of NF1, infiltrative growth pattern, and younger age [14, 45, 47]. In a recent study by Bergamaschi, in a series of 73 pediatric patients (48% with NF1), the presence of two of the following three characteristics—an initially invasive tumor, a short time to relapse, and low probability of secondary complete remission—was associated with an extremely poor prognosis [48]. In our series, one recurrence of tumor growth was detected (case 6), 1 year after surgery.

The most common sequelae after surgical excision of a PNST reported in previous series are pain and neurologic deficit [2, 46]. All four cases with a BPNST had a good outcome with complete resolution of pain after a follow-up period ranging from 2 to 3 years. One of the three patients with a MPNST improved, with resolution of the pain and no residual clinical impairment. The other two patients diagnosed with a MPNST and the patient with Ewing's sarcoma had clinically meaningful, but incomplete resolution of their pain. All patients with motor deficits (cases 1, 2 and 7) improved to M4 level strength after surgical management. Follow-up of two patients (cases 2 and 6) ultimately revealed metastases in both lungs; one of these patients has died, while the other remains in adjuvant treatment.

Conclusions

Analyzing the data acquired, we conclude that certain peripheral nerve tumor characteristics are particularly worrisome, in terms of the risk of initial malignancy or malignant transformation of a known benign nerve sheath tumor. These characteristics include presence or not of NF1; rapid, progressive growth of a stiff mass involving the brachial or cervical plexus or peripheral nerve; increasing pain, especially at rest and at night, which prevents normal activities of the child; extreme tenderness to the point where examining the child is difficult; and a positive Tinel's sign. All such tumors need to be investigated thoroughly. Such clinical presentations must be considered warning signs, especially in patients with NF1, since there is a major risk of malignant-transformation of a PNST and the risk of metastases also increases. In our service, we do not perform preoperative biopsy when clinical and imaging findings suggest a benign tumor, generally assuming a case-by-case posture. When surgery is undertaken, gross total resection is always the goal, including wide margins, especially with malignant tumors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Comitê de Ética em Pesquisa do Hospital Universitário Gaffrée e Guinle 5258) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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