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REVIEW PAPER

Peripheral nerve injuries in the pediatric population: a review of the literature. Part III: peripheral nerve tumors in children

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Abstract

Introduction Peripheral nerve tumors type, inciedence and treatment in the pediatric population should be analyzed.
Methods We have performed an extense literature review of this subject.
Results incidence and distribution are similar to those observed in adults. The most common peripheral nerve tumors in children are neurofibromas and schwannomas. Malignant peripheral nerve sheath tumors are also observed, specially associated with genetic syndromes, like neurofibromatosis and Carney complex.
Conclusion In this review, peripheral nerve tumors have been divided into three categories to aid with understanding: reactive and hyperplastic lesions, benign tumors, and malignant tumors. The most frequent lesions have been described.

Keywords Peripheral nerve tumors · Pediatric population · Neurofibromas · Schwannomas

Introduction

Most peripheral nerve tumors observed in adults can also be found in children. The most frequently observed peripheral nerve tumors in children are neurofibromas, schwannomas, and malignant peripheral nerve sheath tumors (MPNSTs), with neurofibromas and schwannomas accounting for the vast majority of pediatric peripheral nerve tumors [1]. Although some of these tumors occur in isolation, they also may be seen in the context of tumor syndromes, like neurofibromatosis and Carney complex. In this review, peripheral nerve tumors have been divided into three categories to aid with understanding: benign tumors, malignant tumors, and reactive and hyperplastic lesions.

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Benign tumors

Neurofibromas

Neurofibromas are the most common type of benign peripheral nerve tumor [2]. They are of Schwann cells lineage and have either a well-demarcated intraneural or diffuse infiltrative growth pattern [3]. These tumors are composed of the constitutive elements of a normal nerve (Schwann cells and fibroblasts) in addition to perineural-like cells, intercalated with nerve fibers, and embedded in a myxoid matrix. Single or multiple nerve fascicles that enter and leave the tumor can be identified. Axons present within the tumor comprise an important feature that distinguishes neurofibromas from schwannomas [4].

Although many neurofibromas are associated with neurofibromatosis type 1 (NF-1), a sizeable proportion of neurofibromas occur sporadically.

Four classifications of neurofibroma are recognized and defined according to their architectural growth patterns, all of which can be seen in children. They are localized, diffuse, plexiform, and massive soft-tissue neurofibromas [3]. The most common are localized cutaneous neurofibromas; small nodular masses that arise from a small cutaneous nerve. Localized intraneural neurofibromas are deeper focal lesions that may involve major peripheral nerves or a plexus, and typically result in fusiform expansion of the nerve trunk. Plaque-like enlargement of a nerve, usually in the head and

neck region, characterizes diffuse neurofibromas [4]. Localized and diffuse neurofibromas tend to occur sporadically and are not related to NF-1. Together, these two forms comprise 90% of neurofibromas [1]. Diffuse neurofibromas preferentially affect children [5].

Plexiform neurofibromas are multinodular, tortuous, and elongated masses characterized by the involvement of multiple adjacent nerve fascicles or components of a plexus. Their appearance has been described as resembling a "bag of worms" [6]. This subtype is rarely seen as a sporadic lesion; it is almost always associated with NF-1. Plexiform neurofibromas have the potential for malignant transformation. Massive soft tissue neurofibromas represent a very rare subtype, which is characterized by extensive, diffuse infiltration of soft tissue and skeletal muscle, usually causing regional or single-limb enlargement. This subtype is also almost always associated with NF-1.

Schwannomas

Schwannomas are the second most common type of peripheral nerve tumor in children. The majority occur sporadically. They are typically a well circumscribed, encapsulated mass of neoplastic Schwann cell origin [3]. These tumors arise from a single nerve root or peripheral nerve fascicle and grow in an eccentric fashion, progressively displacing uninvolved fascicles [4]. The classical histological architecture of a schwannoma is biphasic with dense compact areas called Antoni A and less-compact areas called Antoni B. Some of the cells may palisade to form Verocay bodies within the Antoni A areas [1].

As stated earlier, in most patients, schwannomas occur sporadically as solitary masses. However, they are also seen as one component of complex disorders, like NF-2, schwannomatosis, Carney complex, and a dominant syndrome associated with multiple schwannomas, multiple nevi, and multiple vaginal leiomyomas [7, 8]. Schwannomas are not associated with NF-1.

Many authors consider schwannomatosis to be a third form of neurofibromatosis. It is characterized by the presence of multiple schwannomas in the absence of the vestibular schwannomas required for a diagnosis of NF-2 [1].

There are other pathological variants of schwannoma, including plexiform, melanotic, and cellular forms. The melanotic subtype is rare, characterized by the marked accumulation of melanin in neoplastic cells and associated melanophages. Unlike other schwannomas, this subtype can become malignant and is associated with Carney complex; in fact, psammomatous melanotic schwannomas are listed as one of the major diagnostic criteria for Carney complex [9].

Perineuriomas

Perineuriomas are uncommon benign tumors composed of differentiated perineurial cells. These tumors stem from cells located in the perineurium of the peripheral nerve, where they form a blood-nerve barrier. They can mimic certain benign and malignant soft-tissue lesions [10], so immunohistochemical and/or ultrastructural confirmation of perineurial cell differentiation is necessary for the diagnosis.

These tumors can be classified into two main types: intraneural perineuromas and extraneural soft tissue perineuromas [4].

Intraneural perineuriomas most often affect patients in the second or third decade of life and appear as fusiform masses along the path of a large nerve (e.g., as localized cylindrical enlargement over a few centimeters) [10]. Affected patients typically present with a slowly progressive, painless swelling of a peripheral nerve associated with gradual loss of motor and sensory function [1]. Progressive muscle weakness, with or without atrophy, is markedly more common than pain or sensory disturbances [11].

Extraneural soft tissue perineuriomas are more frequent than their intraneural counterparts, usually asymptomatic, and tend to occur in middle-aged adults.

Perineuriomas have been reported in children [11–14]. Although, as stated above, most intraneural perineuromas are diagnosed in the second or third decade of life, roughly half of reported patients with a perineurioma started having symptoms prior to adulthood. The diagnosis is generally established late, however, because there is typically no pain and many children remain unaware of the progressive functional impairment that is occurring [11].

Fascicular biopsy may be indicated for a definitive diagnosis; however, in most patients, the clinical pattern, together with the tumor's radiological and surgical appearance, allows clinicians to make the diagnosis without histological confirmation [11, 15].

With respect to treatment, some have advocated resecting and grafting focal lesions; however, tumor resection and nerve reconstruction has proved to be of no benefit, and tendon transfers can be considered for the majority of patients [11, 15].

In any child with a motor deficit involving a single major nerve or plexus as the only meaningful symptom, the possibility of a perineurioma should be entertained during diagnostic workup [11].

Neurothekeomas

Neurothekeomas and nerve sheath myxomas used to be designated as the same tumor. Both are superficial slow-growing tumors that usually are asymptomatic [16]. Contrary to nerve sheath myxomas, however, cellular neurothekeomas have

negative S100 staining, which indicates they are not of Schwann cell origin [17]. Also, contrary to nerve sheath myxomas, neurothekeomas have a predilection for the upper limbs, head, and neck of pediatric and young adult females [18–20].

Nerve sheath myxomas

As just stated, nerve sheath myxomas and neurothekeomas are similar entities that once were mistakenly classified as the same tumor. Now, nerve sheath myxomas are considered to be significantly rarer than neurothekeomas, such that, unlike neurothekeomas, they no longer are deemed to be a significant tumor type within the pediatric population [1].

Ganglioneuromas

Ganglioneuromas are rare tumors that arise from sympathetic ganglion cells. They are large, slow-growing, encapsulated tumors that histologically consist of mature ganglion cells (neurons), axons, satellite cells, Schwann cells, and fibrous stroma [21]. They are considered the benign counterpart of ganglioneuroblastomas and neuroblastomas. The absence of immature elements distinguishes ganglioneuromas from these latter two entities [1].

More frequent in young females, such masses can occur anywhere along the sympathetic nerve chain, though the mediastinum, retroperitoneum, and adrenal glands are common locations [22]. Although usually asymptomatic, they can be associated with specific complaints due to their local mass effect. Malignant transformation has been reported [4].

Ganglioneuromas have been reported in children [23–25].

Malignant peripheral nerve tumors

Malignant tumors affecting peripheral nerves remain a challenge, both diagnostically and therapeutically, and the mechanisms responsible for their development are still incompletely understood. Malignant peripheral nerve tumors can be classified into neurogenic tumors (i.e., malignant peripheral nerve sheath tumors) and non-neurogenic tumors (synovial sarcomas, Pancoast tumors, soft tissues sarcomas, lymphomas, and intraneural metastases) [15]. Non-neurogenic tumors have been reported in adults, but not in children.

Malignant peripheral nerve sheath tumor (MPNST)

Malignant peripheral nerve sheath tumors (MPNST) account for all malignant tumors arising from the nerve sheath of the peripheral nerves. These tumors can arise from any peripheral nerve, but larger nerve trunks—including the brachial plexus, sacral plexus, and sciatic nerve—are the most common sites [26]. They are aggressive soft tissue sarcomas that account for 5–10% of soft tissue sarcomas [27].

A sarcoma is considered an MPNST if it arises within or from a peripheral nerve, or alternatively arises from a pre-existing benign or other malignant nerve sheath tumor. It is also considered an MPNST if it has the appearance of an MPNST in a patient with NF-1 or if it has the appearance of an MPNST and histologic, immunohistochemical, or ultrastructural features suggestive of Schwann cell differentiation [15].

On gross anatomical study, MPNSTs appear whitish-tan to yellow on cut surface and may exhibit necrosis and hemorrhage. Histologic characteristics of these tumors include high cellularity, nuclear atypia, mitotically active spindle cells, abrupt variation in cellularity, and increased perivascular cellularity. Mitotic figures are visualized in more than four per ten high-power fields [1]. Distinction from other sarcomatous lesions is sometimes challenging.

These tumors have no gender or racial associations and tend to occur in patients between the ages of 20 and 50 years. The main risk factor for developing an MPNST is the presence of NF-1, with NF-1 patients accounting for more than half of all MPNSTs [15]. The reported lifetime risk of an individual with NF-1 developing MPNST generally ranges between 2 and 10% [1], with patients having internal plexiform neurofibromas at even greater risk (10–15% of patients' progress to MPNST). NF-1 patients generally develop their MPNST at a slightly younger age than the general population, but the majority of cases still present in adulthood [1, 15]. Most sporadic and all NF-1-associated MPNSTs carry the NF-1 deletion, but the malignant transformation process is still not well understood [1].

Radiation exposure, the other important risk factor for developing an MPNST, is associated with approximately 10% of MPNSTs. On average, radiation-related MPNSTs occur 15 years after radiation exposure (range 4 to 41 years) [15].

In one series, regional lymph node involvement was observed in 9% of patients and distant metastases in 6% [28], but, in another series, a much higher incidence of regional lymph node involvement (31.7%) was evident [26].

Patients usually present with a growing mass and neurological manifestations attributable to the involved neural structure. Magnetic resonance imaging has little value in terms of distinguishing MPNSTs from schwannomas. Positron emission tomography (PET) has been advocated as an adjunct study to identify increased metabolic activity [1].

Gross total resection with wide margins is the preferred primary treatment of MPNSTs and has been shown to be the strongest predictor of overall survival. Sometimes, however, gross total resection is either impossible or associated with significant functional loss due to the resection of adjacent major vessels and/or nerves. Other prognostic indicators are tumor size and the coexistence of neurofibromatosis [26, 29].

Radiation therapy has been used as an adjuvant treatment in cases of MPNST that could not be fully resected to improve local control of the disease. These tumors are usually considered to exhibit uncertain chemosensitivity, but recent evidence suggests that there may be a role for chemotherapy in patients with high-grade histology [26, 29–31].

Roughly 10–20% of patients with MPNSTs present during childhood [32, 33]. In 2014, Bates et al. published their analysis of data on pediatric MPNST patients extracted from the SEER-18 database, a database that provides information on the US population from 1973 to 2009. They identified 165 pediatric-age MPNST patients, ranging in age from infancy to 19 years old. After exclusions, 139 patients in the SEER-18 database met study criteria for outcomes analysis. The overall incidence of MPNST in children under 19 years old was found to be 0.56 per million person-years. No gender or racial associations were observed. Among children, those in their first year of life, those between 1 and 4 years old and those between 5 and 9 years old all exhibited a statistically lower incidence of MPNST than adolescents between the ages of 15 and 19. Median overall survival in the pediatric population was 30 months. On multivariate analysis, only localized disease and treatment with surgery were positive prognostic factors [26]. In another study, among 167 pediatric patients with MPNST, overall 5-year survival was 43–59%, while 5-year progression-free survival was 29–45% [28].

Three cases of MPNST have been reported in children, all 6 to 13 years old, who presented with a primary bone neoplasm in the absence of NF-1 [34].

Reactive and hyperplastic lesions

Neuromas

The most frequent type of pediatric neuroma is a traumatic neuroma that results from a peripheral nerve injury. Other neuromas—like Morton's neuromas, Pacinian neuromas, and palisaded-encapsulated neuromas are extremely rare in this age group.

Morton's neuromas are very infrequent in patients younger than 20 years old [1, 35]. Palisaded-encapsulated neuromas, a non-traumatic type of neuroma, can present in children, though they tend to present in the fifth to seven decades of life [36–38]. Neuromas also can be associated with a variety of syndromes, including multiple mucosal neuroma syndrome and multiple endocrine neoplasia syndrome (MEN 2B). A congenital Pacinian neuroma has been reported [39].

Intraneural ganglion cysts

Intraneural ganglion cysts are non-neoplastic, fluid-filled cystic formations contained within the epineurium of the peripheral nerves. Although many peripheral nerves may be affected, the common peroneal nerve, at the fibular neck, is by far the most frequently affected site [40–42]. This condition is a rare clinical entity in adults, but even rarer in children, with fewer than 70 cases reported in published literature [41, 43, 44].

The pathogenesis of intraneural ganglion cysts remained controversial until Spinner proposed a unifying articular theory [40, 45]. According to Spinner, the formation of intraneural ganglion cysts in a peroneal nerve is a dynamic process that typically starts in a degenerating superior tibiofibular joint and subsequently extends to the nerve along its articular branch in the intra-epineural space via the path of least resistance as determined by pressure fluxes [42]. Surgical management consists of disconnecting the articular branch of the peroneal nerve and decompression, rather than resection, of the cyst.

Excellent surgical results and a favorable prognosis have recently been reported in children, much better than the outcomes typically achieved in adults [41].

Lipomatous tumors

Lipomatous tumors consist of adipose tissue, which either may be encapsulated or infiltrate adjacent neural structures [1]. The spectrum of adipose lesions of nerves is broad, including extra/intraneural lipomas, neural lipomatosis, and various combinations of these two lesions. Lipomatous tumors involving nerves are rare, but have been reported in children [46].

Biopsy is not necessary for the diagnosis of lipomatous tumors because of their pathognomonic appearance on magnetic resonance imaging (MRI). Intraneural lipomas can be resected safely, since they are focal deposits of fat that displace fascicles. However, lipomatosis of major nerves should not be resected because it is a more diffuse process in which fat is inter-dispersed between fascicles [15]. Decompression of the enlarged nerve may be indicated in some cases of lipomatosis.

Neuromuscular choristomas

Neuromuscular choristomas are benign lesions defined by the presence of mature striated muscle within the normal epineurium of a peripheral nerve [1]. These lesions are extremely rare, with only one case reported in a child [47].

Hansen's disease

Hansen's disease, historically called leprosy, can affect children who have lived in or traveled to endemic areas and may cause the tumor-like expansion of peripheral nerves. It is a common chronic infectious condition in the Third World, where it is the most frequently encountered treatable cause

of peripheral neuropathy [48]. Hansen's disease usually presents with dermatologic manifestations and lost sensation in the distribution of affected nerves. Peripheral nerves are always involved and sensory disturbances are the most common clinical manifestation of this condition [48]. The ulnar nerve is the nerve most frequently affected.

In the rare case of pure neuritic leprosy, leprosy may be difficult to distinguish from a true tumor without biopsy. Pathological examination reveals a grossly thickened nerve. Microscopic examination reveals a destructive, inflammatory granulomatous process in the nerve with intense lymphocytic infiltration [48]. Some fascicles may be totally destroyed, while others appear almost normal. Fite's acid fast stain can be used to visualize the offending mycobacteria and confirm the diagnosis; polymerase chain reaction (PCR) testing also is available [49].

With appropriate treatment, nerve inflammation can abate and further neurological impairment may be halted. Existing neurologic deficits will persist, however [1]. Surgical procedures mostly include tendon transfers. Improved sensory function has been reported in some patients following nerve grafts [50].

Conclusions

Peripheral nerve tumors are much the same in children and adolescents as in adults. The most common peripheral nerve tumors in children are neurofibromas and schwannomas. Malignant peripheral nerve sheath tumors are another significant subset of tumors, particularly in the setting of tumor syndromes, especially NF-1. The other lesions described in this review are mostly exceedingly rare and their presentations anecdotal.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interests.

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