ORIGINAL ARTICLE

Management of Head and Neck Plexiform Neurofibromas in Pediatric Patients With Neurofibromatosis Type 1

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Objectives: To identify presenting symptoms, growth patterns, and outcomes of head and neck plexiform neurofibromas (PNs) in children with neurofibromatosis type 1 (NF-1); to determine which patients may benefit most from operative intervention in terms of duration of disease-free progression, perioperative morbidity, identification of malignancy, and symptom relief.

Design: A retrospective review of 39 pediatric patients with NF-1 who had PNs of the head and neck managed at a single tertiary referral center.

Results: Thirty-nine patients had 49 head and neck PNs, 11 small (≤5 cm) and 38 massive (>5 cm and/or involving multiple deep neck sites). Thirty-nine surgical procedures were performed on 18 of 35 patients with massive disease, and 4 procedures were performed on 4 of 11 patients with small tumors. Tumors recurred in 1 (25%) of 4 patients with small tumors and in 18 (100%) of 18 patients with massive tumors ($P=.001$; mean time to regrowth, 3.1 years.)

Conclusions: Size and location of PN tumors most influenced presentation of clinical symptoms. Complete tumor resection was possible only in patients with small PNs. Patients with PNs of the head and neck were more likely to benefit from surgery if the indications were to (1) exclude malignancy in a rapidly enlarging mass; (2) provide relief from neurogenic pain or motor weakness; (3) improve symptoms caused by airway compression; or (4) enhance cosmesis in those with disfiguring disease.

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NEUROFIBROMATOSIS (NF) type 1 (von Recklinghausen NF) is a genetic disorder that occurs in 1 of 4000 births. It is inherited in an autosomal dominant pattern with variable penetrance; however, as many as 50% of cases may result from spontaneous mutation. The disease results from a defect in a tumor suppressor gene on chromosome 17, which leaves affected individuals at risk for developing a variety of benign and malignant tumors.[1]

The most common tumors found in patients with NF-1 are neurofibromas and optic gliomas. Neurofibromas can be of either the plexiform or cutaneous variety. Plexiform neurofibromas (PNs) are typically congenital, with approximately 50% occurring in the region of the head, neck, face, and larynx. The natural history of their growth pattern has not been studied, but they appear to grow in early childhood at variable rates with growth and plateau phases. Plexiform neurofibromas tend to be locally invasive and may result in cosmetic deformities and functional deficits. Histologically, they are peripheral nerve sheath tumors containing all elements of the peripheral nerve and are characterized by an increase in endoneurial matrix with separation of nerve fascicles and proliferation of Schwann cells.[2] Grossly, the tumors are diffuse and infiltrative giving them a classic "bag of worms" appearance. Plexiform neurofibromas exhibit a malignant transformation rate of 4% to 5%.[3] Cutaneous neurofibromas, conversely, appear during preadolescence and have no malignant potential.

Associated features of NF-1 may include vision loss caused by optic pathway tumors, hypertension caused by renal artery stenosis, learning disabilities that appear to be associated with benign spongiform changes of the brain, and various skeletal problems (eg, osseous dysplasia affecting the sphenoid, tibia, and spine). Diagnosis is based entirely on clinical criteria (**Table 1**).[4]

Management of plexiform neurofibromas has traditionally been surgical. These tumors are not radiosensitive and, given their slow growth rates, only limited benefit has been seen with chemotherapy. Needle et al[5] examined the largest series of surgically managed PNs and demonstrated that 54% recur within a 10-year period, with the greatest risk of recurrence found in lesions involving the head and

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neck and in children treated when younger than 10 years. Given this, considerable controversy persists regarding the indications and timing of surgical interventions for PNs of the head and neck. The relatively high rate of local recurrence and the potential for postoperative cosmetic and functional morbidity have left otolaryngologists reluctant to undertake resection. In general, unless the tumor is easily resectable without risk of resultant neurological dysfunction, PNs in children are managed conservatively with serial imaging studies to determine impending risk to the airway or other critical neck structures.

To our knowledge, there has been no large series study of management strategies for PNs of the head and neck exclusively. Herein, we present a series of 39 patients with NF-1 and PNs in the head and neck region who were treated at the Children's Hospital of Philadelphia. Tumors were evaluated with respect to size, nerve of origin, treatment plan, and outcome.

METHODS

We reviewed the outpatient clinic records, operative notes, and pathology and radiology reports of 39 patients with NF-1 diagnosed as having PNs of the head and neck from 1992 to 2003. This study was approved by the internal review board at our institution. The patients in this study represent those with the most severe head and neck disease who were referred to and observed by the Neurofibromatosis Clinic of the Children's Hospital of Philadelphia. The clinic is staffed by a geneticist, neurologist, and oncologist, as well as by various consultants from other services. Patients were observed at varying intervals, depending on the severity of their disease, with visits ranging from monthly to yearly.

Medical charts were reviewed to determine tumor characteristics (size, location, pathologic properties), patient characteristics (age at NF diagnosis and age at first operation), associated symptoms at presentation (cranial neuropathy, airway compromise, and cosmetic deformity), surgical management (extent of resection and indication for surgery), adjuvant interventions (radiation therapy and chemotherapy), and evidence of postoperative tumor progression. Tumors were classified as either small (≤5 cm in greatest diameter) or massive (>5 cm and/or involving multiple deep neck spaces). For the purposes of this study, supportive procedures such as placement of tracheotomy or percutaneous endoscopic gastrostomy tubes were not considered surgical procedures because no tumor was resected.

Benign PNs have a classic radiographic appearance, consisting of a mass with heterogeneous and serpiginous mixed density. In addition, NFs are isointense or hyperintense on T1-weighted magnetic resonance (MR) images and hyperintense on T2-weighted scans. These masses typically enhance with gadolinium.[6]

In most instances, our patients had head and neck scans based on clinical suspicion of a mass. Routine scans of the neck were not performed in asymptomatic patients. Findings suggestive of malignant degeneration include rapid growth in an otherwise stable PN or areas of necrosis within a mass. Extent of surgical resection was defined as near total (>90% of gross tumor removed) or subtotal/debulking (50%-90% of gross tumor removed). Progression was defined as the reappearance of tumor in an operative bed believed to be grossly free of disease at the completion of surgery or regrowth of a partially excised tumor as evidenced by clinical or radiographic criteria.

The *P* value comparing postoperative recurrence rates for children with massive vs small tumors was calculated using the Fisher exact test. Kaplan-Meier survival curves were not performed to compare regrowth rates of subtypes of massive tumors because there were small numbers of patients in each group, and because the dropouts were more likely to be patients lost to follow-up than those who had no tumor regrowth. For analysis of remaining statistics, tumors were treated as individual events rather than by patient because data do not exist that suggest that tumors located at different sites behave similarly.

Table 1. Diagnostic Criteria for Neurofibromatosis Type 1*

The Patient Should Have 2 or More of the Following Indications
≥6 Café au lait spots
1.5 cm or larger in postpubertal individuals
0.5 cm or larger in prepubertal individuals
≥2 Neurofibromas of any type *or* ≥1 plexiform neurofibroma
Freckling in the axilla or groin
Optic glioma
≥2 Lisch nodules (benign iris hamartomas)
A distinctive bony lesion (sphenoid or lone bone dysplasia)
A first-degree relative with neurofibromatosis type 1

*Adapted from Gutmann et al.[4]

RESULTS

PATIENT STATISTICS

Of the 39 patients studied, 25 were male and 14 were female. The mean age of the study patients was 13.8 years (age range, 1.0-24.5 years). The average age at initial diagnosis of NF-1 was 2 years (age range, birth to age 7 years). Most patients presented with café au lait spots and axillary or inguinal freckling; 61% of the study group exhibited a family history of NF-1. Approximately one third of patients had optic glioma or characteristic spongiform brain changes confirmed by neurologic imaging. Average total follow-up time was 10.0 years.

TUMOR SITE

Four of the 39 patients had isolated small PNs of the head and neck, defined as noncutaneous masses no more than 5 cm in greatest diameter. Thirty-five of 39 patients had massive PNs, defined as noncutaneous masses larger than 5 cm in greatest diameter and/or involving multiple deep neck spaces. Three of the patients also had a separate massive lesion at another site. Seven patients had 1 small PN and at least 1 concomitant massive PN (**Table 2**). Of the 4 small isolated PNs, 1 lesion was contained entirely within a sublingual gland, 1 was located in the supraorbital region, and 2 were located on the posterior neck.

The 38 massive PN lesions were categorized by nerve of origin based on radiographic findings. Remarkably, all massive tumors were radiographically determined to be derived from 1 of 3 nerves of origin: the vagus nerve (CN X), the trigeminal nerve (CN V), and cervical spine rootlets. There were 4 vagal tumors, 10 trigeminal tumors, and 24 cervical spine rootlet tumors. In each case, the tumor extended along the length of the suspected nerve of origin, widening its skull base foramina and involving its corresponding deep neck space. When ob-

Table 2. Characteristics of Plexiform Neurofibromas by Size of Tumor

Characteristic	Tumor Size	
	Small (≤5 cm)	Massive (>5 cm)
Patients, No.	11	35
Tumors, No.	11	38
Patients who underwent surgery, No.	4	18
Surgical procedures, No.	4	31
Age at first procedure, mean (range), y	5.0 (4.0-6.0)	8.7 (3.0-20.0)
Common indications	Disfigurement Diagnosis	Pain and/or weakness secondary to tumor mass Dysphagia Airway compromise Concern for malignancy
Immediate postoperative complications	None	Cranial nerve impairment in 3 patients Horner syndrome in 2 patients
Recurrence rate,* %	25 (1/4)	100 (18/18)
Time to recurrence, mean (range), y	3 (3)	3.1 (1.0-6.0)
Follow-up time, mean (range), y	5.4 (3.0-7.5)	8.1 (0.5-13.5)
Interventions before or after surgery	None	Postoperative chemotherapy in 3 patients Postoperative radiation therapy in 1 patient

*P = .001.

served over time, tumors often demonstrated signs of spread into adjacent soft tissue spaces.

SIGNS AND SYMPTOMS

All patients presented to our clinic with a solid mass in the head and neck region. Most often, parents described the lesion as originating as a soft tissue fullness that progressed to a more distinct mass. All small tumors resulted in cosmetic deformity without functional deficit. Impairment of neurologic structures and/or compression to functional head and neck structures were demonstrated only in the massive PN group. Specifically, vagal tumors caused dysphagia and airway compromise. Trigeminal nerve tumors were the most cosmetically disfiguring. Those trigeminal masses in the V2 distribution caused proptosis, while V3 lesions caused dysphagia and airway compromise. Finally, cervical spine rootlet lesions were a source of the most profound neurologic dysfunction and when large enough, caused compressive airway symptoms.

Radiographically, the lesions demonstrated characteristic findings by computed tomography (CT) and MR imaging. Magnetic resonance imaging was the preferred imaging modality unless spinal reconstruction hardware was present. On CT, the masses tended to diffusely infiltrate local tissues and were moderately enhancing when contrast was injected. On MR imaging, the lesions enhanced heterogeneously on T2 scans, and on postgadolinium T1-weighted images, the masses was serpiginous with variable hypodensity. Malignancy was suspected based on radiographic findings of sudden growth in a previously stable lesion or evidence of necrosis.

The cervical spine lesions showed widened cervical spine foramina that often involved several adjacent foramina but rarely exhibited frank spinal cord compression. Those with trigeminal disease had extensive involvement of the parapharyngeal, parotid, and masticator spaces, extending from the skull base to the upper neck. The CT or MR imaging scans demonstrated widening of the foramen rotundum, with tumor involving maxilla and orbit if V2 was the source of tumor. As might be expected, tumors with V3 involvement tended to have masses extending from a widened foramen ovale and were frequently associated with cystic masses of the mandible and marked dental malocclusion. Patients with vagal tumors had extension of disease along the carotid space from the jugular foramen often following the course of the nerve into the mediastinum. These tumors frequently resulted in compressive airway compromise. However, airway impairment was more likely present with massive cervical spine lesions than with vagal tumors.

TREATMENTS AND COMPLICATIONS

Thirty-five procedures were performed on 22 of the 39 patients in this study at The Children's Hospital of Philadelphia. Surgical excision was performed on 4 of 11 patients who had small head and neck PNs. The indication for resection of all but 1 mass in this subset was to improve cosmesis. One small lesion occurring in a sublingual gland was resected for diagnostic purposes. In all cases, near-total resection was undertaken with no evidence of residual gross tumor.

Of the 35 patients with massive head and neck NFs, 18 underwent at least 1 resection (**Table 3**). Patients who did not undergo surgery had similar size tumors. The decision to operate was not based on size criteria, but rather the presence of symptoms. In those patients who did not undergo surgery, there were no mortalities. Patients who opted against surgery and had symptomatic tumors (cosmetically disfiguring disease or severely debilitating and/or life-threatening symptoms such as uncontrollable pain and airway obstruction) were invited to enroll in 1 of 3 chemotherapy protocols. These protocols included a trial using a combination of vinblastine and methotrexate, a trial using farnesyl transferase inhibitor, and trials using interferon alfa with or without cis-retinoic acid or thalidomide to attempt to slow the growth rate of the tumor. Although some of these protocols are ongoing, at the time of publication none has demonstrated efficacy with respect to halting disease progression on a consistent basis.

All procedures in this group were subtotal resections intended only for debulking and biopsy and not for total resection of disease. Two (50%) of 4 patients with vagus tumors underwent a total of 3 surgical procedures; 6 (60%) of 10 patients with trigeminal tumors underwent a total of 11 surgical procedures; and 10 (42%) of 24 patients with cervical spine masses underwent a total of 17 surgical procedures. Plastic surgeons or pediatric otolaryngologists performed neck dissections for vagal tumors and

Table 3. Characteristics of Massive Head and Neck Plexiform Neurofibromas by Nerve of Origin

Characteristic	Nerve of Origin		
	Vagus	Trigeminal	Cervical Spine Rootlet
Patients, No.	4	9	22
Tumors, No.	4	10	24
Patients who underwent surgery, No.	2	6	10
Surgical procedures, No.	3	11	17
Age at first procedure, mean (range), y	8 (6-10)	7 (4-11)	10 (3-20)
Indication	Dysphagia Airway compromise Rapid increase in tumor size	Disfigurement V3: dysphagia and/or airway V1: proptosis	Pain and/or weakness secondary to tumor mass Rapid increase in tumor size Airway compromise
Immediate postoperative complications	None	Permanent facial nerve weakness in 2 patients	Horner syndrome in 2 patients Median and/or ulnar nerve palsy in 1 patient
Time to recurrence, mean (range), y	2 (1-3)	3.6 (2-8)	3 (1-6)
Follow-up time, mean (range), y	11 (11)	6.3 (2-12.5)	8.5 (0.5-13.5)
Interventions before, during, or after surgery	Perioperative chemotherapy–no change in growth rate	None	Perioperative chemotherapy–no change in growth rate

either maxillectomy, mandible resection, or parotidectomy for trigeminal tumors. Most cervical spine rootlet tumors were debulked by neurosurgeons performing either posterior triangle dissections or spinal fusion procedures. Mean ages of first attempted resection for vagal, trigeminal, and cervical spine masses were 8 years (age range, 6-10 years), 7 years (age range, 4-11 years), and 10 years (age range, 3-20 years), respectively. A decision to operate on vagal tumors was made based on progression of symptoms, including dysphagia and airway compromise, and in 1 patient because there was a concern for malignancy in a rapidly growing mass. Trigeminal nerve PNs were resected based on symptoms of disfigurement, dysphagia, airway compromise, and ophthalmologic dysfunction. Neurologic symptoms, including upper and lower extremity pain or weakness, were the most common indications for surgery in the cervical spine subset, accounting for 12 (70%) of 17 surgical procedures. Other indications included airway impingement (3/17, 18%) and concern for malignancy in a rapidly growing mass (2/17, 12%).

Of all patients observed, there were no perioperative mortalities. No postoperative morbidity was observed in the vagal tumor resections. However, permanent (>2 years) facial nerve weakness was seen as a sequela of trigeminal tumor resection in 2 of 6 patients. Of the 10 patients who underwent resection for cervical spine tumors, Horner syndrome (ptosis, miosis, and anhidrosis) resulted in 2 patients. In addition, cervical spine and brachial plexus dissection resulted in median and ulnar nerve impairment in 1 patient. A tendon transfer was performed to rehabilitate the brachial plexus injury. No rehabilitative procedures were performed to correct the 2 cases of mild facial weakness.

RECURRENCE AND/OR DISEASE PROGRESSION

One (25%) of 4 small PNs recurred during a mean follow-up of 5.4 years (follow-up range, 3.0-7.5 years), while 18 (100%) of 18 massive PNs recurred during a mean follow-up of 8.1 years ($P=.001$, Fisher exact test). Specifically, tumor regrowth in 1 small tumor of the supraorbital region was observed in the third postoperative year. No additional treatments were undertaken.

All tumors in the massive PN subset ultimately demonstrated regrowth. On average, vagal tumors recurred at 2 years, trigeminal masses at 3.6 years, and cervical spine rootlet PNs at 3 years after surgery. Multiple surgical procedures were performed on 1 of 2 vagal masses, 5 of 6 trigeminal lesions, and 5 of 10 cervical PNs. Perioperative chemotherapy, performed in 2 cervical spine cases and 1 vagal PN case, did not slow or stabilize progression of disease.

A total of 5 procedures were undertaken over concern for malignancy in a rapidly growing mass (1 small PN, 3 cervical PNs, and 1 vagal PN). Malignancy was found in 2 of the 5 patients (ages 12 and 15 years), both with long-standing histories of large PNs. Both had a PN with histologic foci of malignant fibrosarcoma within a large benign mass. In each case, total gross excision was attempted with postoperative external beam radiation. At 1- and 6-year follow-up, the patients have not demonstrated recurrent malignant disease. It should be noted that malignancy was not incidentally found in any patient in whom it was not preoperatively suspected, nor has it developed in any of our patients who originally were not selected for surgery. Overall, the malignancy rate for the entire study group was 2 (5%) of 39 patients, an incidence similar to that reported in prior studies.

CASE PRESENTATIONS

Case 1

Patient 1 is a 7-year-old girl who first presented at age 2 months with biphasic stridor. Imaging revealed massive bilateral cervical spine PNs that caused bilateral external compression of the subglottic airway, visualized by endoscopy (**Figure 1**A). She required urgent placement of a tracheostomy tube at the time of diagnosis because her airway was narrowed by greater than 50 percent of the subglottic space. In addition, her swallowing

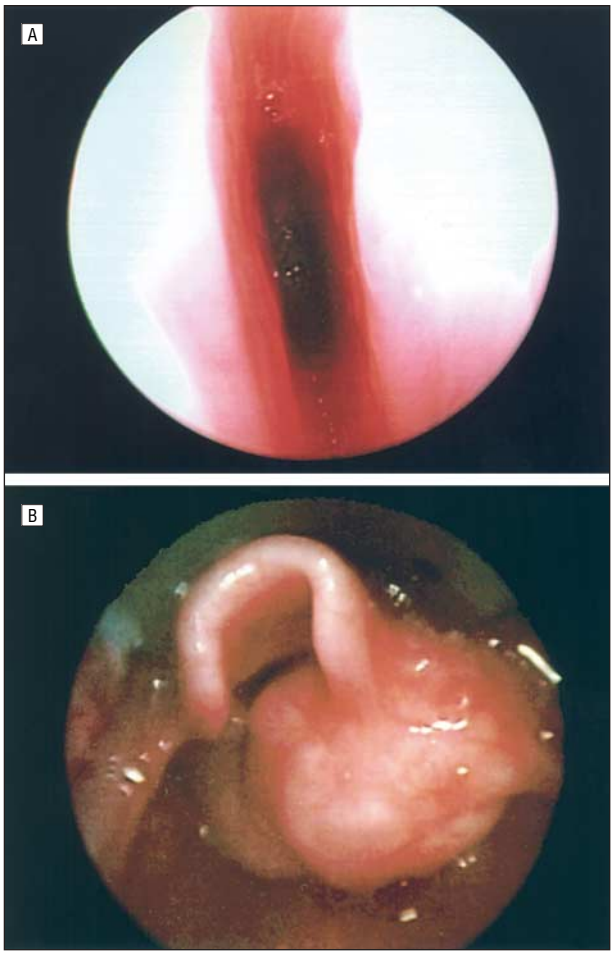

Figure 1. Endoscopic images from patient 1, a 7-year-old girl with bilateral paraspinal plexiform neurofibromas. A, Compression resulting in greater than 50% subglottic stenosis. B, Large plexiform in her right supraglottis that developed at age 4 years.

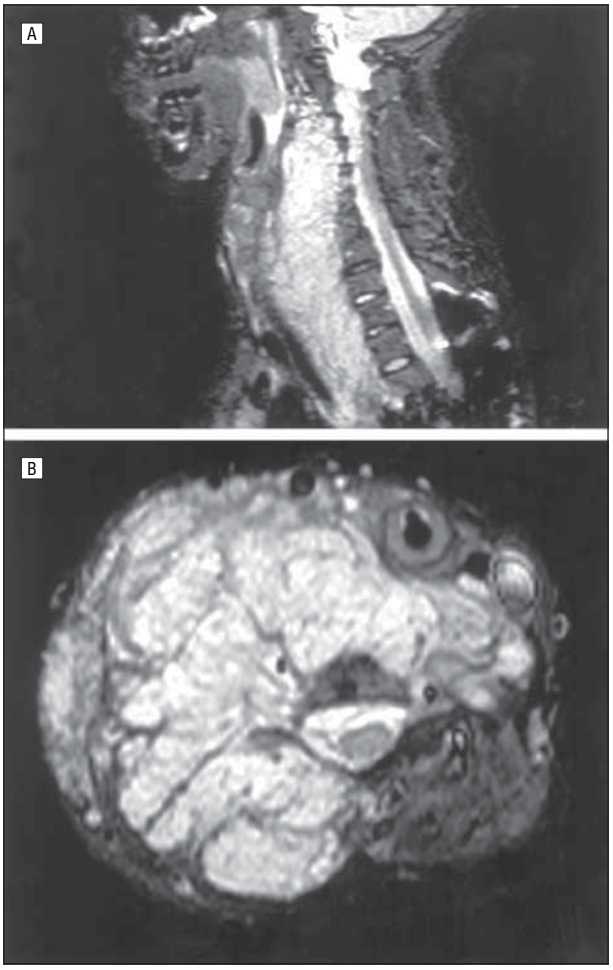

Figure 2. Patient 2, a 13-year-old boy, had a massive right-sided plexiform neurofibroma originating from the cervical spine. A, T2-weighted magnetic resonance (MR) image in the sagittal plane reveals a massive tumor extending from skull base to mediastinum, with frank tumor invasion of the foramina of C2 through C6. B, T2-weighted MR image of the axial plane demonstrating large tumor burden throughout the neck (greater on the right side than on the left) with resulting airway deviation.

was affected to the point that she required percutaneous endoscopic gastrostomy tube placement.

By age 4 years, she developed a large PN in her right supraglottis (Figure 1B). No extirpative surgery was undertaken owing to concern over the potentially large operative morbidity. Chemotherapy has been tried with little or no regression of disease.

Case 2

Patient 2 is a 13-year-old boy with a massive right-sided PN originating from the cervical spine. On T2-weighted MR imaging, a massive tumor was found extending from the skull base to the mediastinum, with frank tumor invasion apparently originating from the foramina of C2 through C6 (**Figure 2**A). In addition, axial imaging demonstrated large tumor burden throughout the neck (greater on the right side than on the left) with resulting airway deviation.

Remarkably, he experienced only mild airway symptoms, and results of his sleep studies were essentially normal. With the advent of neuromotor weakness of his brachial plexus, he underwent tumor debulking for spinal cord decompression and fusion. At 2-year follow-up, his symptoms were stable despite regrowth of tumor as demonstrated on follow-up imaging.

Case 3

Patient 3 is a 7-year-old girl who presented to our otolaryngology clinic at age 7 months with a large left-sided neck mass and café au lait spots on her right neck (**Figure 3**A). She later developed an optic glioma. She experienced mild apneic symptoms at night. In addition, she had a history of intermittent stridor, which was managed supportively. Her MR image demonstrated a massive enhancing plexiform mass within the carotid sheath space with extension to the skull base. The ipsilateral carotid artery was patent but displaced anteriorly (Figure 3B). She underwent trials of chemotherapy with limited improvement, but was relatively asymptomatic at last follow-up and is being treated conservatively. It is believed that the potential morbidity from attempting surgical resection in this region far outweighs the potential clinical benefit, given her mild symptoms and the relatively unpredictable growth rate of these tumors.

COMMENT

In this study, we collected data from the largest series to date of PNs specific to the head and neck. Our goals were to identify symptoms at presentation, growth patterns of tumor, and outcomes based on tumor size and location. In addition, we sought to identify a subset of patients for whom operative intervention optimized outcome, given that large PNs are not amenable to complete extirpation and that regrowth of disease is certain. This decision-making algorithm must reconcile the risks of perioperative morbidity with the goals of identifying previously undiagnosed malignancy, relieving neurologic and compressive symptoms, and addressing cosmetic deformity.

Size and location of the PN most influenced presentation of clinical symptoms. Small tumors were confined to 1 neck space that was superficial and resulted in the appearance of unsightly masses. Massive PNs more commonly invaded multiple deep neck spaces and produced functional symptoms due to neurologic impingement and mass effect on the alimentary and/or respiratory passages.

Interestingly, all large head and neck tumors in our series appeared radiographically to be derived from 1 of 3 nerves of origin: vagus, trigeminal, or cervical spine rootlets. Trigeminal nerve PNs, as expected, were the source of the most profound disfigurement in our patients, especially those in the V2 distribution (which caused ophthalmologic symptoms such as proptosis) and V3 lesions (which most commonly led to swallowing and airway problems and dental malocclusion). Vagal tumors tended to extend from the skull base to the mediastinum, causing dysphagia and airway compromise owing to their close proximity to the pharynx, esophagus, and trachea. Finally, cervical spine rootlet masses were found to compress the airway and cause neurologic impairment, especially in the distribution of the brachial plexus (C5-T1). Regardless of nerve of origin, imaging demonstrated greater tumor burden than patient symptoms would suggest, with most tumors showing skull base involvement and extensive infiltration throughout multiple tissue planes.

Subtotal resection of massive tumors, as opposed to total extirpation, was attempted owing to the anticipated profound morbidity associated with the latter approach. Regardless of tumor site, first surgical procedures were performed when the patient was roughly in the preadolescent age range. All massive head and neck PNs regrew, with disease-stable intervals comparable among all massive subtypes (approximately 3 years). By that time, reappearance of tumor was evident, often with recurrence of symptoms. Multiple procedures were pursued in all subsets, but most frequently in the patients with cervical spine PNs, who often required multiple spinal and/or brachial plexus decompressions. Perioperative morbidity, while not demonstrated in the small PN group, manifested in the subset of patients with massive tumors in the form of Horner syndrome in 2 patients, facial nerve weakness in 2 patients, and ulnar and median nerve dysfunction in 1 cervical spine case.

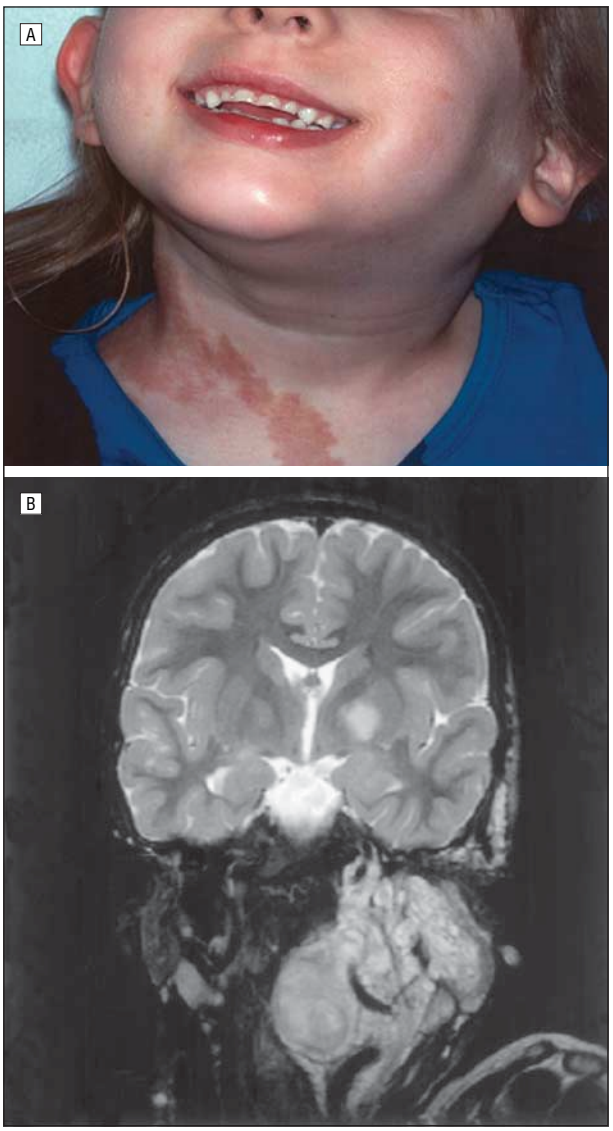

Figure 3. Patient 3, a 7-year-old girl, had a large, left-sided neck mass. A, Color photograph clearly shows the café au lait spots on her right neck; B, T2-weighted magnetic resonance image in the coronal plane demonstrates a massive enhancing vagal plexiform mass within the carotid sheath space with extension to the skull base. The ipsilateral carotid artery is patent but displaced anteriorly.

Other authors have reviewed management strategies for patients with PNs both in a general sense and with regard to the head and neck subsite specifically. Greinwald et al[1] reported a series of 3 patients with massive pediatric head and neck PNs, all of whom underwent aggressive resection. According to the authors, acceptable indications included significant disfigurement, potential neurovascular compression, or impending aerodigestive obstruction. They advocate careful preoperative planning, with procedures performed only if complete or nearly complete resection seems possible in the context of preservation of function. To this end, a variety of approaches to the parapharyngeal space were performed along with conservation laryngeal surgery. No recurrence was seen in any of the 3 patients at 3-year follow-up.

In our series, all patients with massive PNs had significant involvement of areas such as the skull base, pre-

cluding total excision with acceptable morbidity. Furthermore, even our patients who had extensive debulking procedures had predictable regrowth of disease within a few years of surgical intervention. Although the surgical treatment stabilized symptoms in many cases, the tumors continued to slowly grow.

In 2002, Wise et al[7] described a single patient who underwent subtotal resection of a massive pediatric PN in an effort to explore the vexing issue of surgical timing. Acknowledging the inevitability of functional disturbance when surgical resection of massive lesions is undertaken, their recommendation was to delay resection as long as the lesion is asymptomatic. Their illustrative patient had a tracheostomy tube in place for airway protection over the long term, and definitive resection was attempted only after other symptoms developed, including headache, facial pain, dysarthria, and increased tumor growth rate. In our experience, while significant short-term improvement in cosmesis or symptoms can be achieved with radical resection, the apparent universal phenomenon of eventual recurrence must be understood by both patient and family prior to embarking on attempted resection of massive lesions.

Finally, Needle et al[5] reported a large series of 121 patients with PNs at several locations on the body in an attempt to identify prognostic indicators of recurrence. Patient age younger than 10 years, lesion location on the head, neck, or face, and less extensive resection were all associated with a shorter interval to progression. Our study looked solely at patients with PNs of the head and neck. The only long-term recurrence-free intervals were seen in patients whose lesions were 5 cm or smaller and in whom resection was believed to be total at the time of surgery. Disappointingly, regardless of apparent nerve of origin, massive PNs within the head and neck were almost all seen to recur within 3 years of initial surgery, with an overall freedom from progression of 0% at 10 years.

The goals of current studies using chemotherapy are to slow or stop progression of existing disease. The rationale for using the combination of methotrexate and vinblastine is based on findings that desmoid tumors (aggressive fibromatosis) are similar to PNs, and several small studies have shown favorable objective results using this combination of agents on desmoid tumors.[8,9] The rationale for using farnesyl transferase inhibitors is that high levels of this enzyme are found in PNs.[10] Interferon alfa has been used with and without retinoic acid and thalidomide as antiangiogenesis and antineoplastic agents, but these therapies have limited efficacy (unpublished data, 2005).

Our study constitutes the largest case series of PNs of the head and neck in pediatric patients. In our experience, small lesions of the head and neck are most amenable to total resection with acceptable perioperative morbidity and low long-term recurrence rates. Massive lesions, while demonstrating 3 distinct patterns of clinical presentation and growth, all behave similarly in terms of difficulty of achieving total resection and overall short interval to tumor regrowth and reappearance of symptoms. Nevertheless, surgery is the only modality that has been shown to achieve at least temporary control of tumor growth and symptom progression.

In this context of certain tumor progression, there exist nonetheless certain indications for surgical debulking of massive lesions: (1) most importantly, to exclude malignancy in a rapidly enlarging plexiform mass; (2) to address airway compromise, particularly when it cannot be alleviated by tracheostomy alone; (3) to alleviate or stabilize symptoms caused by compression of neural structures, particularly in paraspinal tumors that seemed to respond well to spinal decompression procedures; and (4) to improve cosmesis, especially in patients with trigeminal tumors, bearing in mind the associated risk of facial nerve palsies.

Our experience at the Children's Hospital of Philadelphia has underscored the critical importance of adopting a multidisciplinary approach to the management of these complex cases. Looking ahead, we know that a multicenter, natural history study of these tumors is under way that will hopefully allow for better insight into timing surgical interventions. Clearly, the future of successful control of PNs lies in the development of effective nonsurgical modalities. No chemotherapeutic agent has yet been identified that reduces the size of these tumors. In the short term, careful examination of past experience may assist the clinician in selecting patients most amenable to successful surgical intervention.

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