Pediatric Plexiform Neurofibromas: Impact on Morbidity and Mortality in Neurofibromatosis Type 1

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Objective To characterize morbidity, mortality, and surgical outcomes in pediatric patients with symptomatic plexiform neurofibromas (PNFs).

Study design We conducted retrospective analysis of data from clinical records of surgical history and other neurofibromatosis type 1 (NF1)-related complications in children with PNFs seen at Cincinnati Children's Hospital Medical Center between 1997 and 2007.

Results A total of 154 children with NF1 and PNFs were identified. Children with symptomatic PNFs had increased incidence of other NF1-related tumors ($P < .05$). Patients with NF1 and PNFs had a higher mortality rate (5/154, 3.2%) when compared with patients without or with asymptomatic PNFs (2/366, 0.5%; $P = .024$). The most common morbidities leading to surgeries were neurologic, disfigurement, orthopedic, and airway complaints. Less extensive resection predicted a shorter interval to second surgery ($P < .0019$). The highest recurrence was seen in tumors located in the head, neck, and thorax ($P < .001$).

Conclusions These findings quantify the increased risk for additional tumors and mortality associated with symptomatic PNFs. Surgical interventions were required in many cases and resulted in added morbidity in some cases. Patients with PNFs were more likely to benefit from surgery when the indications were airway compression or disfigurement. *(J Pediatr 2012;160:461-7)*.

Neurofibromas are benign peripheral nerve tumors that occur sporadically or in patients with the autosomal dominant syndrome neurofibromatosis type 1 (NF1).[1] NF1 is one of the most common genetic diseases, affecting approximately 1 in 3000 newborn infants.[2,3] Plexiform neurofibromas (PNFs) are neurofibroma variants in which tumor cells spread along multiple fascicles of the nerve, leading to a diffuse mass of thickened nerve fibers surrounded by proteinaceous matrix.[4] PNFs can be deep or superficial in location or a combination of the two.[5] Because symptoms related to PNFs depend on tumor size and location, the decision to treat is complex. Characterization of the morbidity, mortality, and surgical outcomes is necessary to improve care for affected patients.

PNFs are thought to be congenital and occur in 25% to 50% of children with NF1.[6] PNFs can transform to malignant peripheral nerve sheath tumors (MPNSTs) with an estimated lifetime risk for patients with NF1 of approximately 10%.[4,7-9] Furthermore, large PNFs can compress vital organs and can result in severe morbidity and even death. Surgical excision of PNFs is currently the only established therapy, but is rarely curative. Most of these tumors are invasive and not amenable for complete resection. Research advances in NF1 are increasing our understanding of the biology of PNFs; several potential therapeutic targets have been identified.

Evidence-based treatment of patients with NF1 is often difficult because of the complexity of cases and varied disease spectrum. This study provides detailed clinical characteristics and surgical outcomes in a large cohort of pediatric patients with NF1 and symptomatic PNFs.

Methods

A total of 520 patients with known NF1 seen between 1997 and 2007 at the Neurofibromatosis (NF) Center at Cincinnati Children's Hospital were identified. Inclusion criteria for this study included a diagnosis of NF1 on the basis on National Institutes of Health consensus criteria and identification of PNFs clinically or by imaging before the age of 18 years. Clinical data was abstracted from medical charts and entered in a protected database for analysis. Patients are observed for many different indications in this clinic and therefore represent a broad

MPNST	Malignant peripheral nerve sheath tumor
MRI	Magnetic resonance imaging
NF	Neurofibromatosis
NF1	Neurofibromatosis type 1
PNF	Plexiform neurofibroma

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clinic-based population of NF1. However, patients with more complicated needs may have been more likely to be referred to the clinic because of its reputation in treating patients with complicated NF1. Patients were observed at least annually at the NF clinic. Routine screening for PNFs with magnetic resonance imaging (MRI) or other modalities was not obtained on patients observed in the clinic; rather, it was generally ordered on the basis of clinical symptoms. Likewise, routine genotyping of all patients was not obtained. Institutional review board approval was obtained for this study.

Abstracted information included baseline tumor characteristics, age at diagnosis of NF1 and of PNFs, sex, family history, ethnicity, NF1 mutations analyses, PNF anatomical location, number of anatomical locations involved by tumors, malignancies, and symptoms. It was not always clear whether large, complex PNFs arising from multiple nerve routes would count as one tumor or multiple; therefore, PNFs were counted as multiple when they involved more than one anatomical location. PNF morbidity was classified as physical disfigurement, neurologic deficits, orthopedic complaints, airway difficulties, gastrointestinal complaints, genitourinary complaints, and other.

Surgical History and Intervention

Additional information was obtained from the 96 patients who underwent surgical intervention for PNFs during the 10-year follow-up period, including symptoms leading to surgery and physical examination performed by a clinical geneticist during routinely scheduled follow-up appointments at the NF Center. The investigators reviewed all available imaging, and tumor size was estimated on the basis of radiology reports. PNF resections were classified as subtotal when the extent of the surgery was between 50% and 80% of the tumor size and partial resection when the size was <50% of the tumor size. Surgical outcomes were based on patient report of symptoms and tumor recurrence, which was defined as tumor re-growth leading to a second surgery. New symptoms were also evaluated after surgical intervention to establish the risk for complications and adverse outcomes from surgeries related to PNFs. Only patients with documented post-surgical follow-up were included in this analysis.

Statistical Analyses

Baseline clinical characteristics and post-surgical outcomes were analyzed in patients with NF1 and PNFs. To characterize this population, we used basic descriptive statistics (frequencies for dichotomous measures and medians for continuous measures). To determine whether the frequencies of outcomes differed in groups, we performed χ^2 goodness-of-fit tests and the two-sample median test as appropriate. Kaplan-Meier curves were calculated, and log-rank tests were used to compare differences in recurrence-free survival curves on the basis of tumor anatomical location and extent of resection.

Results

Most patients (473/520, 91%) resided in the NF clinic catchment areas of Ohio, Indiana, and Kentucky. Nine percent of the patients (47/520) were referred from outside these states. Patients were Caucasian (80.5%), African American (13.6%), biracial (3.8%), and Hispanic (1.2%), reflecting the NF1 population of greater Cincinnati. Prevalence of known/symptomatic PNFs in our cohort was 30% (154/520 patients). Median patient age at detection of PNFs was 5.5 years (range, 0-18 years). NF1 mutation analysis was performed in only 15% of the individuals with NF1 (78/520) at the Medical Genomics Laboratory, University of Alabama at Birmingham. Nonsense mutations were significantly more likely to be identified in patients with symptomatic PNFs (14/26, 53.8%) when compared with patients without known/asymptomatic PNFs (6/52, 11.5%; $P = .0018$); however, the sample sizes were small. The prevalence of macrocephaly, headaches, and scoliosis (even when corrected by PNF location) were significantly increased in patients with NF1 with symptomatic PNFs compared with patients without known PNFs ($P < .05$; Table I).

PNF Distribution and Age at Presentation

A total of 368 PNF tumors were identified in our population (mean, 2.4 tumors per patient). Of the 154 patients with PNFs, 60% had two or more PNFs in different anatomical locations. The most frequent location of the PNFs was the head and neck (38%), followed by extremities (22%), and trunk (17%; Figure 1, A). PNFs were suspected clinically on the basis of symptoms or obvious deformity in 133 patients (86.4%), and incidental diagnosis was made in 21 patients (eg, chest radiography). All 154 patients underwent MRI confirmation of clinical or incidental imaging abnormalities. A subset of 20 patients without known PNFs who underwent trunk MRI for concern of tumors had normal findings. PNFs located in the head and extremities were identified during all pediatric ages, but most were identified before 6 years (Figure 1, B). Less common tumor locations, such as symptomatic mediastinal PNFs, were only identified during infancy. Age at PNF identification had a bimodal distribution: during early childhood (birth-3 years, 52%) and during adolescence (11-18 years, 22%; Figure 1, C). Subjects with multiple (>4) tumors were more likely to receive a diagnosis before age 3 years ($P = .01$).

Other NF1-Related Tumors and Mortality

A subset of 59 subjects (38.3%) had additional NF1-related tumors, including optic nerve gliomas (n = 37, 24%), other central nervous system gliomas (n = 14, 9%), MPNST (n = 4, 2.6%), neuroblastoma (n = 3, 2%), and a ganglioneuroma (n = 1, 0.7%; Table I). MPNSTs were associated with a known PNF in all cases. Pheochromocytomas were not seen in this cohort of pediatric patients with NF1. NF1 patients with PNFs had a higher incidence of NF1-related

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