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18-Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) Evaluation of Nodular Lesions in Patients With Neurofibromatosis Type 1 and Plexiform Neurofibromas (PN) or Malignant Peripheral Nerve Sheath Tumors (MPNST)

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Abstract

Background—Individuals with Neurofibromatosis type 1 (NF1) are at risk for developing malignant peripheral nerve sheath tumors (MPNST), which frequently arise in preexisting plexiform neurofibromas (PN). Magnetic resonance imaging (MRI) with volumetric analysis and 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) were utilized to monitor symptomatic nodular lesions.

Procedure—Patients with NF1 and PN on a NCI natural history trial were monitored for total body tumor volume (TTV) using volumetric MRI. FDG-PET was performed in individuals with a nodular well-demarcated lesion $\geq$ 3 cm if they were growing, painful, or there was a prior history of MPNST (target lesions). Asymptomatic nodular lesions were evaluated as non-target lesions.

Results—Fifteen patients (8m, 7f) median age of 18.3 years (range, 10–45 years) had a single target and non-target (n = 46) nodular lesions identified on MRI. Target lesions arose within (n = 8) or outside (n = 3) a PN, and all but 1 had increased FDG uptake. FDG uptake was increased in non-target lesions but to a lesser degree. FDG uptake in the surrounding PN was low, similar to background activity. Pathologic evaluation performed in 11 patients demonstrated neurofibroma (n = 6), atypical neurofibroma (n = 2) and malignancy (n = 3).

Conclusions—Nodular target lesions identified on MRI in individuals with NF1 and PN demonstrate increased FDG uptake similar to MPNST, but may be benign on biopsy. Nodular target lesions may be at greater risk for malignant transformation, but their biologic and clinical

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behavior has not been well studied. Careful longitudinal evaluation will be required to better understand the malignant potential of these lesions.

Keywords

18-fluorodeoxyglucose-positron emission tomography (FDG-PET); malignant peripheral nerve sheath tumors (MPNST); neurofibromatosis; plexiform neurofibromas (PN)

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder characterized by distinct clinical features [1,2] including the development of benign and malignant tumors of the nervous system. Plexiform neurofibromas (PN) are benign nerve sheath tumors involving multiple nerve fascicles. They typically have a complex shape, grow more rapidly in young children, and can cause substantial morbidity such as pain, functional impairment, and compression of vital structures [3]. Based on magnetic resonance imaging (MRI), PN are characterized as superficial or deep, invasive or displacing, and fascicular–nodular or diffuse [4,5]. Standard treatment of PN is limited to surgical resection.

Malignant peripheral nerve sheath tumors (MPNST) account for 5–10% of soft tissue sarcomas. Approximately 50% of MPNST are diagnosed in patients with NF1 and the lifetime risk of MPNST in NF1 is 8–13% [6,7]. The peak incidence occurs at a younger age in patients with NF1, generally in adulthood (ages 20–50 years) with 10–20% of cases reported in the first two decades of life. MPNST often arise in a preexisting PN representing malignant transformation [7,8]. Heterogeneous enhancement on MRI and loss of the central dot sign, a central low intensity focus seen on postcontrast MRI imaging characteristic of PN, raise concern for malignant degeneration [3], but MRI alone cannot reliably separate MPNST from a PN. Symptoms related to a MPNST may overlap and can be difficult to distinguish from the growth of a benign PN as patients often present with an enlarging mass, radicular pain, paresthesia, motor weakness, or other neurologic symptoms with both conditions. Complete surgical resection is the only curative treatment for MPNST. In several series, the 5-year overall survival rates for patients with a MPNST ranged 21–52% and appeared to be worse for those with NF1 [6,9–11]. Early detection of malignant transformation of a PN is thus an important goal.

18-Fluorodeoxyglucose-positron emission tomography (FDG-PET) has been shown to be a valuable tool in detecting malignant lesions such as MPNST in patients with NF1 with a sensitivity ranging 89–100%, specificity 72–95%, negative predictive value 95–100%, and positive predictive value 50–71% [12–14]. One study documented a statistically significant difference ($P < 0.001$) in the maximal standard uptake value (SUV_{max}) for MPNST as compared to benign lesions, $12 \text{ g/ml} \pm 7.1$ versus $3.4 \text{ g/ml} \pm 1.8$, respectively. Utilizing an SUV_{max} of 6.1 g/ml as a threshold value, MPNST were distinguished from benign lesions with a sensitivity of 94% and specificity of 91% ($P < 0.001$) [15]. Several studies found that an elevated SUV_{max} could predict for malignancy with mean values of 5.4–7.0 g/ml associated with malignant lesions and 1.5–2.0 g/ml measured with benign tumors. However, there was a range of SUV_{max} values (2.5–3.5 g/ml) in which both benign and malignant

lesions were detected [14,16–18]. The time of FDG injection to PET imaging in these studies was 45–90 minutes though one group evaluated delayed imaging (hour 4) and felt this a more sensitive time point in detecting MPNST [14,18]. FDG-PET has also been evaluated as a measure to predict growth rate of PN and as a prognostic tool for long-term survival in NF1 patients with MPNST [19,20].

We used MRI with volumetric analysis to monitor PN volume in patients with NF1 on a natural history protocol. In a subset of patients we identified not previously described nodular lesions on MRI concerning for MPNST. In order to further evaluate these lesions patients underwent FDG-PET and biopsies of these lesions.

METHODS

Patients 35 years of age with a diagnosis of NF1 by National Institutes of Health (NIH) Consensus Conference criteria or *NF1* mutation analysis were eligible for enrollment on the National Cancer Institute (NCI) NF1 natural history protocol. The NCI has an active clinical trials program for NF1 related tumor manifestations, in particular PN and MPNST. Most patients referred to the NCI for participation in a treatment trial or the natural history trial have unresectable PNs with the potential to cause morbidity. All enrolled individuals with a history of 1 PN or a history of MPNST underwent a detailed clinical evaluation including signs and symptoms of NF related tumors, whole-body MRI, and MRI of their known PN at baseline and longitudinally. Identification of nodular target lesions on MRI as described below resulted in further evaluation with FDG-PET and these patients are the subject of this report. The study was approved by the NCI Institutional Review Board prior to subject enrollment. Informed consent was obtained from subjects or their legal guardians according to Department of Health and Human Services Guidelines.

Whole Body MRI and Volumetric MRI Analysis

Each patient was evaluated for total body tumor volume (TTV) using whole body MRI with volumetric MRI analysis. Patients were imaged in supine position using an integrated body coil and short T1-inversion recovery (STIR) sequence. Axial and coronal images with a slice thickness of 5–10 mm with no skip between slices were obtained in several series in accordance with the maximum range of table movement with overlap between series to allow alignment. Semi-automated volumetric MRI analysis was performed as previously described to evaluate TTV [21], and to monitor the volume of PN. Total tumor volume was defined as the sum of the volumes of all neurofibromas 1 cm.

In addition, the number and volume of nodular lesions were monitored. Nodular lesions were defined as 3 cm, well demarcated lesions on MRI lacking the central dot sign typical for PN (Fig. 1) [22]. Lesions were defined as nodular target lesions if they occurred in a patient with a history of prior MPNST, occurred in absence of prior MPNST history, but were associated with new pain, growth of the nodular lesion exceeding the growth of the surrounding or adjacent PN, or a history of prior abnormal FDG-PET study. Other nodular lesions present were identified as nodular non-target lesions. Follow up MRI of the PN and nodular target and non-target lesions were performed as clinically indicated every 6 months to 2 years.

18-Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) Scan

Positron emission tomography scans utilize a radioactive tracer, in our patients 18-fluorodeoxyglucose, to detect metabolically active tissues including areas of malignancy. The FDG compound was administered as an intravenous, slow push, injection at doses of 15 mCi for adults and 0.11 mCi/kg for children. Patients were allowed nothing by mouth except for water for at least 6 hours prior to the injection. A serum glucose level was obtained within 2 hours of the FDG injection and documented at the time of the scan. Images, from base of the skull to either the upper thighs (older patients), the lower thighs (younger patients) or extending to the sole of the feet, were obtained approximately 60–90 minutes from the time of FDG injection. A CT scan was performed in parallel to aid in FDG localization and attenuation correction. SUV_{max} normalized by body weight (g/ml) of the nodular target and non-target lesions were determined. FDG-PET avid lesions were defined as those areas with increased uptake as compared to standard normal values indicating increased metabolic activity. In addition, background FDG uptake of the surrounding PN, which did not appear nodular on MRI, was determined depending on the location of the PN in three locations: neck/chest, lumbar area, and sciatic nerve area.

Pathology Evaluation

Core biopsies of nodular target lesions, those with increased growth rate, pain, or FDG uptake, were performed for pathologic confirmation if clinically feasible. When possible multiple core biopsy samples were taken and were directed at abnormal areas as seen on imaging. A grading system for nonrhabdomyosarcomatous soft tissue sarcomas described by Parham [23] was utilized combining principles of adult sarcoma grading systems and integrating clinical and morphologic features of pediatric tumors. Cellularity, mitoses per high-power field and degree of necrosis were used to histologically grade tumors I–III.

RESULTS

Of 103 patients enrolled on the NF1 natural history study, 81 (79%) had PN identified on whole body MRI. Of these patients, 15 (7 female, 8 male; median age 18.3 years) were identified as having a nodular target lesion and underwent at least 1 FDG-PET (Fig. 2). In addition, 46 nodular non-target lesions were identified. Indications for FDG-PET were either a history of prior MPNST ($n = 4$) or a nodular target lesion without history of prior malignancy ($n = 11$), but with a history of a prior abnormal PET ($n = 1$), growth of a nodular target lesion within a PN ($n = 6$), or both pain and growth of a nodular target lesion ($n = 4$).

Baseline MRI and FDG-PET characteristics of neurofibromas are shown in Table I for patients with prior MPNST and Table II for patients with nodular target lesions without a history of prior malignancy. Evaluated patients had substantial TTV with a median volume of 1,908 ml (range 1,859–6,800 ml) for patients with a prior MPNST and 2,520 ml (range 83–8,649 ml) for patients without prior MPNST. Growth of the nodular target lesions exceeded growth rate of the PN in which they arose or of adjacent PN in all cases with a 10–538% change in volume per year. In patients who underwent FDG-PET without history of a prior malignancy, growth of the nodular target lesion occurred within ($n = 8$) or outside ($n =$

3) a PN, but without growth of the remaining PN. Three of four patients with a prior MPNST had growth within a PN.

All 15 patients had increased FDG uptake in the nodular target lesion with a median SUV_{max} of 5.3 g/ml (range 2.4–19.5 g/ml), and in all but 2 patients (patient 12 and 13 had SUV_{max} of 2.7 and 2.4 g/ml, respectively) FDG uptake in the nodular target lesion was ≥ 4 g/ml. Eleven of the 15 patients with FDG-PET avid nodular target lesions had additional avid non-target nodular lesions seen, 8 patients had ≥ 3 PET avid lesions while 7 patients had <3 lesions. FDG uptake was also noted in nodular non-target lesions, but was less with a median SUV_{max} of 3.7 g/ml (range, 1.4–12.3 g/ml). FDG uptake in the surrounding PN was low (median SUV_{max} 1.2 g/ml, range 0.5–2.2 g/ml) in all patients, similar to adjacent normal structures.

Biopsies of nodular target lesions were performed in all but four patients: one patient (patient 3) with a prior completely resected low grade MPNST, one (patient 12) with stable uptake on repeat PET imaging, one (patient 2) with a relatively low SUV_{max} in the target lesion and one (patient 15) who was felt to be at too high risk for biopsy related complications. Pathology demonstrated a benign neurofibroma in six patients, atypical neurofibroma in two patients, and malignancy in three patients; two were found to have MPNST (patients 1 and 10) and the third an angiosarcoma (patient 9). Median SUV_{max} values were elevated within each group of patients with nodular target lesions regardless of pathology as compared to the background PN (Fig. 3). Those with a confirmed malignancy or atypical features were noted to have a higher mean SUV_{max} compared to patients who did not undergo biopsy, or who had a diagnosis of a benign neurofibroma on biopsy. Two patients (patients 12 and 15) were monitored clinically and with follow up radiographic imaging and not considered to have a malignant lesion, but a biopsy was not performed.

Eight patients had ≥ 2 FDG-PET scans and MRI studies at the same time. FDG uptake remained constant in three patients in follow up ranging 7–14 months (patients 2, 3, and 7). Five patients had additional abnormalities seen on FDG-PET. In one patient with a prior MPNST a distant site of recurrence was suspected by increasing FDG uptake in a nodular target lesion, SUV_{max} increased from 5.1 to 9.3 g/ml (patient 1). Malignant disease was confirmed on pathologic evaluation of biopsy material (Fig. 4). One patient developed a new lesion on FDG-PET and a previously imaged non-target nodular lesion demonstrated increased SUV_{max} uptake (2.8–4.6 g/ml) and increased size on MRI (patient 8). The patient underwent resection of the lesion and pathology was benign neurofibroma. A third patient with a history of prior MPNST had new lesions on FDG-PET concerning for recurrence (patient 4). A biopsy was not performed at that time, but the patient later developed multiple sites of relapse detected clinically. The remaining two patients demonstrated increased SUV uptake of known lesions and they have been closely followed (patients 5 and 6).

DISCUSSION

PN in patients with NF1 are at risk for transformation to MPNST [7]. Distinguishing between a benign PN and an MPNST can be difficult as the presenting symptoms are often identical and include pain, growth, and/or neurologic deficits. This can be particularly

problematic in children and young adults, a time known to be a peak growth period for neurofibromas [24].

FDG-PET has been evaluated as a method of detecting malignant lesions in NF1 patients and in previously reported series has been shown to be both a sensitive and specific test using qualitative evaluation [14,16]. However, as a quantitative measure correlating an absolute SUV_{max} to pathologic diagnosis, the utility of FDG-PET is less clear. Ferner et al. [14] evaluated 105 patients with NF1 and symptomatic PN utilizing FDG-PET. Of 34 FDG avid sites, 28 malignant lesions were reported (26 MPNST and 2 other malignancies). The SUV_{max} for all malignant lesions was > 2.5 g/ml. Of the remaining six lesions, four were benign PN and two were atypical neurofibromas. A substantial number of these patients ($n = 3$, 50%) had a $SUV_{max} > 3.5$ g/ml. Although the difference in mean SUV_{max} of PN (1.5 ± 1.06 g/ml) as compared to MPNST (5.7 ± 2.6 g/ml) reached statistical significance, between the ranges of 2.5–3.5 g/ml SUV_{max} there were seven benign PN and six MPNST detected. Warbey et al. [18] reported of 36 FDG avid lesions, 21 were MPNST (11 low grade, 10 high grade), 9 atypical neurofibromas and 6 PN. There were no malignant tumors with $SUV_{max} < 3.2$ g/ml, but all six benign tumors presented with a $SUV_{max} > 3.5$ g/ml. Delayed imaging at hour 4 was a more sensitive measure of malignancy, though currently this is not the standard FDG-PET procedure at most centers. In pediatric patients delayed imaging may not be feasible due to risks of prolonged fasting and sedation.

The focus of our study was on the evaluation of FDG-PET in NF1 patients with clinically concerning nodular target lesions identified on MRI, a cohort that has not previously been defined and described in the literature. These lesions were identified by a growth rate exceeding that of the surrounding or adjacent PN based on volumetric MRI analysis, pain, or both. In contrast to the surrounding PN, which demonstrated FDG uptake of 0.5–2.2 g/ml similar to adjacent structures and similar to the uptake of FDG in PN described by Ferner [14,16] of 1.5–2.0 g/ml, the nodular target lesions had increased FDG uptake of 2.7–19.5 g/ml. The SUV_{max} values of all but one nodular target lesion were similar to those previously documented in MPNST, but on biopsy both benign and malignant lesions were detected. Overall there was significant overlap in SUV_{max} values between benign PN, atypical neurofibromas and malignant lesions.

Due to the small number of patients included in this study, we were not able to statistically correlate SUV_{max} values with pathologic diagnosis from biopsy samples. However, 5 of the 11 biopsies performed identified either malignancy ($n = 3$) or atypical neurofibromas ($n = 2$), which were recently identified as precursor lesions of MPNST [25]. Nodular target lesions as defined here may thus be at greater risk for malignant transformation and will require careful longitudinal clinical and imaging monitoring. FDG-PET demonstrated nodular lesions in addition to the target lesion in most patients and many had increased FDG uptake compared to the surrounding PN; however, less than the uptake in target lesions. Careful clinical evaluation, MRI analysis for the presence and growth rate of target lesions compared to that of the surrounding PN, and FDG-PET evaluation would identify lesions of greatest concern to be biopsied. Cumulative radiation exposure should be considered when conducting serial imaging of concerning lesions in patients with NF1. A body weight based, low dose CT radiation protocol and weight-adjusted doses of FDG were utilized at our

imaging center to decrease radiation exposure, but this should also be factored into the decision to perform a biopsy. New imaging modalities such as PET/MRI scans may offer a potential solution to this issue in the future [26].

In summary, increased growth rate of nodular lesions based on volumetric MRI analysis and increased FDG uptake compared to surrounding PN on FDG-PET suggest differences in the biology of nodular lesions and PN, and raises the concern that nodular lesions may be at greater risk for malignant transformation. FDG-PET imaging cannot confirm the presence of a benign PN from a MPNST in all patients, but is one modality that may aid in detecting malignant transformation. Therefore, those patients with nodular target lesions should undergo careful longitudinal clinical and imaging monitoring using MRI and FDG-PET. An increase in SUV_{max} should prompt further investigation or intervention. As complete surgical resection of MPNST is currently the only curative treatment, early biopsy and surgical intervention may be required. The NF1 natural history trial will be expanded to enroll and monitor additional patients with nodular lesions in order to perform the longitudinal studies required to better understand the clinical behavior of these lesions and the utility of FDG-PET scans. We plan to evaluate additional imaging techniques and perform careful analysis of biologic and genetic changes in these lesions to better characterize the biology and malignant transformation.

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Fig. 1. Coronal (A) and axial (B) STIR MRI images of two nodular lesions (arrows) within a neck PN (A) and outside of a pelvic (B) PN. These lesions are well demarcated and lack the central dot sign characteristic of PN.

Fig. 2. Patient 6 with a nodular target and non-target lesions within a PN on composite MRI (**A**) and FDG uptake on corresponding PET scan (**B**). FDG uptake of the PN surrounding the nodular lesion was similar to normal tissue.

Fig. 3. SUVmax (g/ml) values based on histology for patients with target nodular, FDG-PET avid lesions of clinical concern as compared to uptake in non-target nodular lesions and surrounding PN.

Fig. 4. Patient 1 with a history of MPNST and a growing nodular lesion within a PN on axial and coronal MRI scan and increasing FDG uptake on corresponding PET scan. Pathology of this lesion was consistent with recurrent MPNST.

TABLE I.

Patients Who Underwent FDG-PET Imaging Due to History of a Prior MPNST

Pt.	Location	Nodular target lesion			Pathology	Nodular non-target PET avid lesions		Plexiform neurofibromas	
		SUV _{max} (g/ml)	Vol.(ml)	Vol.change (% per year)		No. of lesions	SUV _{max} (g/ml)	Background SUV _{max} (g/ml) ^a	TTV (ml):TTB vol./BSA
1	Left lower extremity	7.2	58	NA	MPNST	7	2.7–6.7	0.67–2.1	6,800:1.85
2	Right pelvis	3.9	35.6	–6	No Biopsy	10	1.7–4.6	0.76–1.8	1,908:1.8
3	Left posterior thigh	3.0	71	NA	No Biopsy	0	NA	0.86–1.49	1,859:1.84
4	Left forearm	8.8	99	NA	NF	4 ^b	2.1–12.3	0.8–1.4	NA
	Median	5.6	85			5.5			1,908
	Range	3.0–8.8	71–356			0–10			1,859–6,800

NA, not available; FDG-PET scan performed at outside institution and SUV not recorded or target lesion could not be measured by volumetric MRI; FDG-PET, fluorodeoxyglucose-positron emission tomography; MPNST, malignant peripheral nerve sheath tumors; SUV_{max}, maximal standard uptake value; vol., volume; TTV, total body tumor volume; BSA, body surface area; NF, neurofibroma; PN, plexiform neurofibromas.

^aBackground PN SUV measurements made in three locations: paraspinal PN found in the neck and chest, paraspinal L spine, and the sciatic nerve (thigh). Additional background measurements were made in the identified nodular (target) lesions as seen on MRI scan

^bFDG-PET of torso only.

TABLE II.
Patients Who Underwent FDG-PET Imaging Due a Prior Abnormal PET Scan or a Growing, Painful Nodular Target Lesion

Pt.	Location	Nodular target lesion			Pathology	Nodular non-target PET avid lesions		Plexiform neurofibromas		
		SUV _{max} (g/ml)	Vol.(ml)	Vol. change (% per year)		No. of lesions	SUV _{max} (g/ml)	Background SUV _{max} (g/ml) ^a	TTV (ml):TTB vol./BSA	
5	Presacral	10.8	50	10	Atypical NF	2	4.9–5.6	0.5–2.2		2,705:1.93
6	Right psoas	8.1	98	NA	NF	5	2.4–5.7	0.78–0.99		3,755:1.73
7	Right neck	4.4	13	71	NF	4 ^b	2.0–4.4	1.4–1.87		NA
8	Left pelvis	9.4	86	42	Atypical NF	2	3.3–3.6	0.7–1.5		2,335:1.99
9	Right pelvis	19.5	372	70	Angiosarcoma	5	1.9–6.0	0.98–1.6		NA
10	Left posterior thigh	4.0	86	538	MPNST	3 ^b	1.4–8.8	1.0–1.4		8,649:1.61
11	Abdominal mass	4.1	12	137	NF	0 ^b	NA	1.15–1.5		83:1.37
12	Left pelvis	2.7	11	NA	No biopsy	0 ^b	NA	1.9		802:1.25
13	Left thigh	2.4	62	132	NF	0 ^b	2.0	0.84–1.5		3,757:1.2
14	Right posterior thigh	6.4	113	24	NF	0 ^b	NA	2.0		3,162:1.61
15	Left submandibular	5.3	33	16	No biopsy	3 ^b	4.9–5.7	1.26–1.34		2,283:1.57
	Median	5.3	62	70		2				2,520
	Range	2.4–19.5	11–372	10–538		0–5				83–8,649

NA, not available; FDG-PET scan performed at outside institution and SUV not recorded or target lesion could not be measured by volumetric MRI; FDG-PET, fluorodeoxyglucose-positron emission tomography; MPNST, malignant peripheral nerve sheath tumors; SUV_{max}, maximal standard uptake value; vol., volume; TTV, total body tumor volume; BSA, body surface area; NF, neurofibroma; PN, plexiform neurofibromas.

^aBackground PN SUV measurements made in three locations; paraspinal PN found in the neck and chest, paraspinal L spine, and the sciatic nerve (thigh). Additional background measurements were made in the identified nodular (target) lesions as seen on MRI scan

^bFDG-PET of torso only.