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CLINICAL STUDY-PATIENT STUDIES

The role of [18F]-fluorodeoxyglucose positron emission tomography in predicting plexiform neurofibroma progression

Michael J. Fisher · Sandip Basu · Eva Dombi · Jian Q. Yu · Brigitte C. Widemann · Avrum N. Pollock · Avital Cnaan · Hongming Zhuang · Peter C. Phillips · Abass Alavi

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Abstract *Background* The role of FDG–PET for managing patients with plexiform neurofibromas (PN) is unclear. While many PN tumors exhibit periods of rapid growth, others grow slowly or unpredictably and may have periods of relative quiescence. The ability to predict which PN are likely to progress should facilitate a more timely initiation of medical treatments. Since conventional radiographic techniques have limited prognostic value, the use of a functional imaging modality to predict tumor progression is desirable. We hypothesized that PN tumors with high metabolic activity as demonstrated by FDG–PET are more likely to progress in the following year. *Methods* All patients were clinically stable, but were considered at high-risk for progression based on anatomical location of PN. FDG–PET scans were performed within two weeks of the baseline MRI study. Standardized uptake values (SUV) were calculated for all focally active index lesions and analyzed for correlation with changes in quantitative MRI over the ensuing year. *Results* Fifteen of the 18 enrolled patients showed various degrees of FDG uptake as focal abnormalities, and these abnormalities corresponded to those noted on the MRI scans. Thirteen patients and 19 lesions were evaluable for PN volume change. The SUV-max ranged from 0.9 to 4 (median 1.5). There was a significant difference in the percent increase in PN volume in the following year for lesions that had an SUV > 2 compared to those with lower values ($P = 0.016$). *Conclusions* These findings support the hypothesis that FDG–PET imaging predicts PN growth rate, and, therefore, may assist clinician decision making with regard to treatment of PN and enrollment in clinical trials.

Keywords FDG · Fluorodeoxyglucose · MRI · Neurofibroma · Neurofibromatosis type 1 · NF1 · PET · Plexiform · Positron emission tomography

M. J. Fisher (✉) · P. C. Phillips
Division of Oncology, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104, USA
e-mail: fisherm@email.chop.edu

M. J. Fisher · A. N. Pollock · A. Cnaan · H. Zhuang · P. C. Phillips · A. Alavi
University of Pennsylvania School of Medicine, Philadelphia, PA, USA

S. Basu · J. Q. Yu · H. Zhuang · A. Alavi
Division of Nuclear Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

E. Dombi · B. C. Widemann
Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD, USA

A. N. Pollock
Department of Radiology, The Children's Hospital of Philadelphia, Philadelphia, PA, USA

A. Cnaan
Division of Biostatistics and Epidemiology, The Children's Hospital of Philadelphia, Philadelphia, PA, USA

Introduction

Neurofibromatosis type 1 (NF1) is a common genetic disorder which occurs in both familial and sporadic forms. The gene has been localized to the long arm of chromosome 17 (17q11.2) [1–3]. Neurofibromas are the most common tumor associated with NF1, and the plexiform neurofibroma (PN) subtype represents a major cause of morbidity. The development of clinical trials for PN has identified the need for a rational approach to identify those

PN likely to progress. While many lesions exhibit periods of rapid growth, others grow slowly or inconsistently and may have periods of relative quiescence [4]. The ability to predict which PN will progress would improve decision making with regard to treatment of PN and enrollment in clinical trials. Currently, magnetic resonance imaging (MRI) is primarily used to detect disease progression; and most clinical trials are using volumetric MRI analysis to more sensitively monitor changes in PN volume over time [5]. However, individual MRI studies cannot be used to predict which tumors are likely to progress. Therefore, the identification of physiological or biological predictors of PN progression is crucial.

Clinically aggressive tumors often have a high metabolic rate and are more likely to progress. Positron emission tomography (PET) utilizing [18F]-2-fluoro-2-deoxyglucose (FDG) is able to detect levels of glucose metabolism throughout the body [6–8]. Studies of the utility of PET in musculoskeletal tumors, including neurofibromas and malignant peripheral nerve sheath tumors, have shown a high correlation between tumor grade and uptake of FDG [9–12]. FDG–PET studies [13, 14] of benign musculoskeletal tumors and optic gliomas reveal that metabolically active lesions are more likely to progress. We, therefore, hypothesized that FDG–PET may be an important imaging modality to differentiate benign PN which are aggressive and will progress from those that will stay stable. Predicting the rate of growth of these tumors would facilitate early intervention in tumors with a high probability of progression.

Methods

Patient population

Subjects with NF1, less than 30 years of age, without radiographic evidence of PN progression but at high-risk for progression as defined by one of the following:

(1) Anatomic location of PN such that progression carries a high-risk of significant impairment of function, pain, or disfigurement. Typical locations include neck/mediastinum, paraspinal nerve roots, orbit, and face.
(2) Tumors which the patient, family or caregiver believe have increased in size during the preceding year, but appear stable by standard clinical or radiographic measures.

Patients with small (<2 cm) PN without functional impairment or pain and those being enrolled on a chemotherapy trial and/or have a history of prior treatment of their PN with chemotherapy were excluded. Subjects were recruited from the Neuro-Oncology Clinic at The Children's Hospital of Philadelphia. All patients or their legal guardians were required to sign a document of informed consent prior to study entry. This study was approved by the Institutional Review Board of The Children's Hospital of Philadelphia. No management decisions were made based upon the PET results. No subjects underwent biopsy during the study period.

Imaging procedures

MRI

MRI was performed soon after enrollment and one year following the baseline examination. Multiplanar TSE T2-weighted or short T1 inversion recovery (STIR) images were acquired and quantitative evaluation of PN size was measured using a method of automated volumetric MRI analysis previously described [15]. Percent change in PN volume from baseline to follow-up scan was calculated.

FDG–PET

Soon after enrollment, whole body FDG–PET imaging was performed 60 min after the intravenous injection of 0.14 mCi/kg of FDG. Emission and transmission data was acquired with successive overlapping axial frames. Transmission scans were performed for all patients to provide attenuation correction with a ^{137}Cs point source. Three dimensional acquisition technique was adopted which allows use of a lower dose of radiotracer. The ordered-subsets expectation maximization (OSEM) method was used to reconstruct all PET images.

Study analysis

PET qualitative evaluation

Two experienced nuclear medicine physicians blinded to the clinical and radiological information independently evaluated each study. Any area of increased uptake was identified and rated on a five point visual scale: no uptake, uptake equal to the adjacent normal soft tissues, mildly increased uptake, moderately increased uptake and markedly increased uptake. The anatomical location of the lesion was recorded. If the two readers agreed in the interpretation of the scans, the reading was considered to

be final. If the two readers disagreed, a consensus reading determined the final interpretation of the scan.

PET quantification

After image reconstruction, a region of interest (ROI) was carefully drawn to include the entire area of abnormal FDG uptake. Subsequently, contiguous PET scan slices were examined and the maximum standardized uptake value (SUVmax) was calculated. SUVmax was automatically generated (ADAC^{TM}, Milpitas, CA) using the standard approach by dividing the activity concentration in the four pixels with maximum activity in the ROI drawn around the lesion by the injected dose divided by the body weight [16].

Statistics

FDG–PET data at study entry were analyzed for association with changes that were detected in quantitative MRI over the ensuing year. A Spearman correlation was calculated between the baseline SUVmax and the percent change in PN volume. In addition, a cutoff SUVmax of ≤ 2 vs. >2 was used to group the observations into low uptake versus higher uptake (based on Ferner et al. [10]), and the percent change in PN volume was compared between the two groups using a two-sample Wilcoxon rank-sum test. We predicted that tumors with a higher likelihood of growth within one year are the ones with an SUV > 2 at baseline, based on data published by Ferner et al. [10]. In their study, of fifteen benign PN, five underwent a surgical procedure. While the indication for surgery was not stated, surgery is usually reserved for more aggressive/symptomatic PN. The mean SUV for lesions that were resected ("progressive") was 2.04 compared with 1.29 for lesions that did not require surgery ("stable"). Of note, none of the unresected PN increased in size during a 3–26 months period of observation. Our study had approximately 80% power to detect a correlation of 0.60 or higher, or to detect a probability of 0.08 that an observation in the SUVmax ≤ 2 group will have a lower growth percent change in PN volume than an observation in the SUVmax > 2 group, while controlling for $\alpha = .05$. A *P*-value of 0.05 was used to define significance.

Results

Eighteen patients whose ages ranged from 6 to 27 years (mean 14.4 years; only 2 patients >17 years) were enrolled in this research study; all were considered "high-risk for progression" based upon anatomic location of PN (see "Methods"). These included nine males and nine females. The most common sites of involvement by PN were the face and neck (Table 1). Fifteen of 18 patients (83%) showed various degrees of FDG uptake as focal abnormalities. The location of FDG–PET abnormalities in these patients corresponded to that noted on the MR scans. Thirteen cases and 19 lesions were evaluable for PN volume change at one year and form the basis of this report (Table 2). Four patients were lost to follow-up and one has not yet had quantitative MRI analysis and therefore were not included in the final analysis. The SUVmax was calculated for all index lesions ($N = 19$) and values ranged from 0.9 to 4.0 (mean 1.67, median 1.5). Most lesions had low SUV comparable to other relatively, metabolically-inactive low-grade soft tissue and musculoskeletal tumors [10, 12, 17, 18], which further corroborates the benign nature of these tumors.

We evaluated the relationship between SUV and tumor progression by searching for the presence of both a direct correlation as well as a threshold effect. We found a moderate direct correlation between SUVmax and change

Table 1 Clinical characteristics of enrolled subjects

Subject	Age (years)	Gender	Index lesion(s)
1	7	M	Left face/neck/ear/skull
2	14	M	Right supraclavicular and left neck
3	13	F	Right neck
4	15	F	Left neck and right neck
5	15	F	Left neck
6	17	F	Right temporal/cheek
7	6	M	Left neck/skull
8	9	F	Left upper arm, left axilla, and left chest
9	27	F	Right pelvis/buttock
10	10	F	Right chest, left neck, and pelvis
11	17	M	Right neck/chest/axilla and left axilla
12	16	F	Right flank/back
13	17	M	Bilateral pelvis
14	12	M	Right neck/skull and left neck
15	10	F	Left neck/shoulder
16	20	M	Right proximal thigh, left chest, right pelvis, and upper cervical spine
17	17	M	Left supraclavicular and cervical spine
18	17	M	Pelvis, right neck/axilla and left neck/axilla

M, male; F, female

Table 2 Positron emission tomography findings and change in plexiform neurofibroma volume for evaluable index lesions

Subject	Index lesion(s)	Qualitative uptake	SUVmax	% Change in PN volume
1	Left face/neck/ear/skull	3	1.3	13
2	Right supraclavicular	5	4.0	32
	Left neck	4	1.8	8
3	Right neck	4	2.0	0.6
4	Left neck	1	1.5	0
	Right neck	1	1.3	4
5	Left neck	2	1.7	1
6	Right temporal/cheek	2	0.9	3
7	Left neck/skull	1	1.0	9
8	Left upper arm	3	1.0	4
	Left axilla	4	2.1	30
	Left chest wall	3	1.4	3.6
9	Right pelvis/buttock	3	2.1	16
10	Right chest	4	1.9	63
	Left neck	4	1.6	16
	Pelvis	3	1.2	23
11	Right neck/chest/axilla	3	1.5	−0.6
12	Right flank/back	3	1.1	2
13	Bilateral pelvis	3	2.4	23

Qualitative uptake scale: 1 = no uptake, 2 = background, 3 = mild, 4 = moderate, 5 = severe/intense

SUVmax, maximum standardized uptake value; %, percent; PN, plexiform neurofibroma

in PN volume over the subsequent year (Spearman correlation = 0.41, $P = 0.083$, Fig. 1). We found a significant difference in the percent increase in PN volume in the following year for lesions that had an SUV > 2 ($n = 4$, median percent change = 27%) compared to those with lower values ($n = 15$, median percent change = 4%) ($P = 0.016$, Fig. 2). A representative case exemplifies the potential usefulness of PET for evaluation and monitoring of the patients with PN (Fig. 3).

Discussion

Plexiform neurofibromas (PN) are the second most common complication of NF1 (after learning disabilities) [19] with an incidence of 16.8–39% in NF1 patients [20–22]. These benign tumors are composed of axons, Schwann cells, fibroblasts, perineural cells, mast cells, collagen fibrils, and extracellular matrix. They form along branches of nerves, nerve plexus, or spinal nerve roots, and often

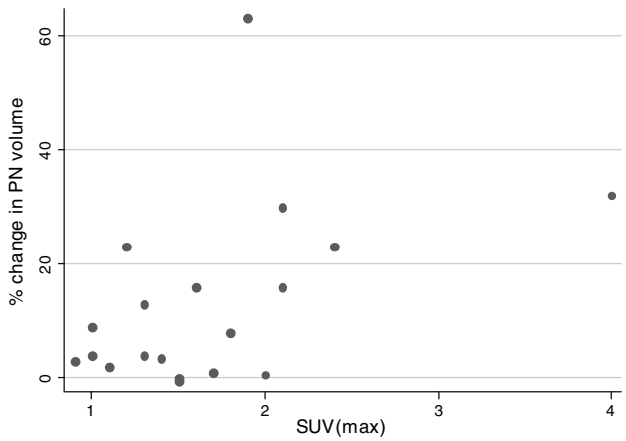

Fig. 1 Scatter plot of percent (%) change in plexiform neurofibroma (PN) volume and standardized uptake value (SUVmax). There is a moderate direct correlation between SUVmax and change in PN volume over the subsequent year (Spearman correlation = 0.41, $P = 0.083$)

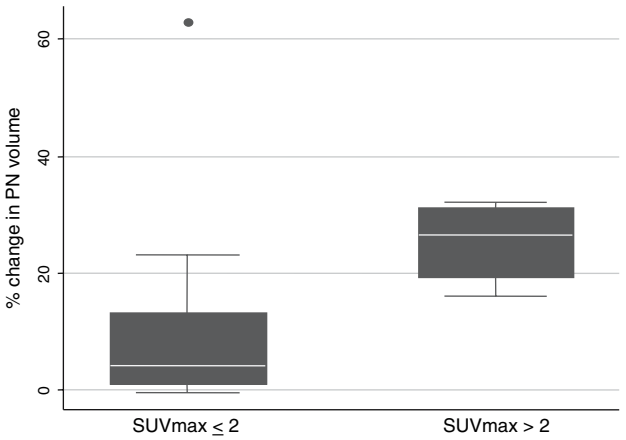

Fig. 2 Percent (%) change in plexiform neurofibroma (PN) volume for lesions with maximum standardized uptake value (SUVmax) ≤ 2 and those with SUVmax > 2. There is a significant difference in the percent increase in PN volume in the following year for lesions with an SUVmax > 2 compared to those with lower values ($P = 0.016$, two-sample Wilcoxon rank-sum test)

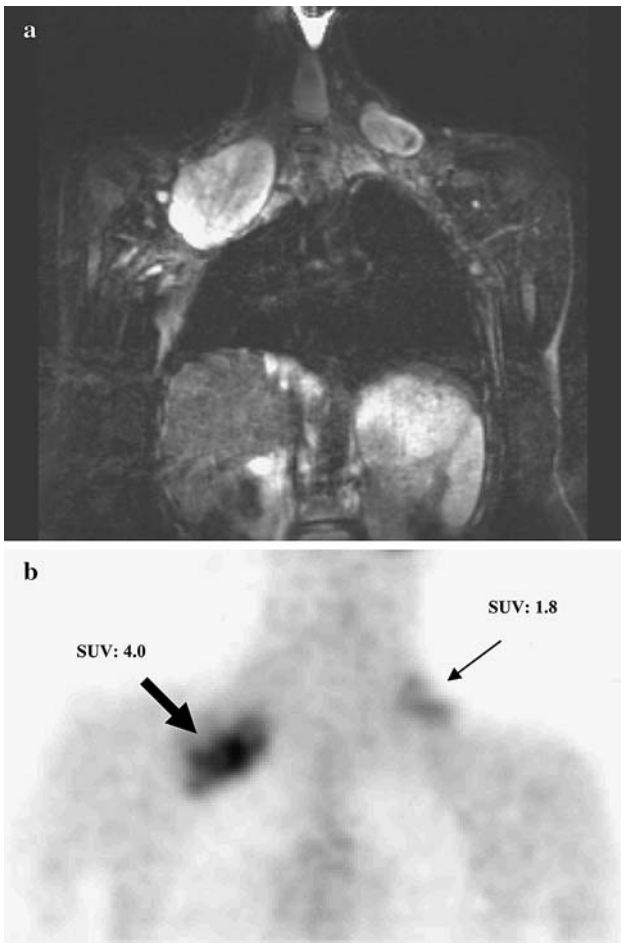

Fig. 3 Subject 2. MRI (**a**) reveals a large plexiform neurofibroma (PN) in the right brachial plexus and a smaller PN in the left lower neck. The intensity of [18F]-2-fluoro-2-deoxyglucose (FDG) uptake (**b**) is high on the right side (SUVmax = 4.0), while the lesion on the left has relatively low uptake (SUVmax = 1.8). In the following year, the right-sided PN progressed (increase in volume of 32%), while the PN on the left changed minimally, consistent with a minimally active process

involve multiple fascicles of a nerve [4]. They are at risk for malignant degeneration to malignant peripheral nerve sheath tumors (8–13% lifetime risk) [23]. While malignant transformation is rare, benign PN represent a major cause of serious morbidity in NF1 resulting in pain, impaired function, and disfigurement. They may become life-threatening by mechanical compression of vital organs such as the trachea, great vessels, or spinal cord, and may significantly interfere with normal function when located in the extremities or orbit [22, 24].

While many PN tumors exhibit periods of rapid growth, others grow slowly or unpredictably and may have periods of relative quiescence. Current clinical trials for PN require MRI evidence of increased tumor volume over a time period of less than 12 months for enrollment. The ability to predict which PN tumors are likely to progress should facilitate a more timely initiation of appropriate therapies (i.e. before the tumor has grown larger and caused significant impairment). Since conventional radiographic techniques have limited prognostic value, the use of a functional imaging modality to predict tumor progression is desirable in this setting. Prior reports of FDG–PET imaging in patients with NF1 include single case reports of increased FDG uptake in malignant peripheral nerve sheath tumors (MPNST) [25–28] and a larger series ($N = 16$) correlating SUV and survival in patients with MPNST [29].

Two series used FDG–PET to differentiate benign PN from MPNST [10, 30]. Ferner et al. [10] calculated SUV for 20 PN suspicious for malignant change and found a significant difference in mean SUV between the malignant and benign tumors, although there was a range of SUV values (2.7–3.3) where there was overlap between benign and malignant tumors. Cardona et al. [30] examined 25 neurogenic soft tissue tumors in 13 patients (5 with NF1) and found that FDG–PET distinguished between malignant peripheral nerve sheath tumors and benign neurogenic tumors with 100% sensitivity and 83% specificity.

The present investigation is the first prospective study of FDG–PET to evaluate PN that do not have clinical or radiographic features generating a clinical suspicion of malignant change. All cases had "benign" PN (i.e. none were progressive at study entry or had clinical features suggestive of malignant transformation) and were found to have a low SUVmax at study entry. The range of SUV values are comparable to those reported in the largest previously published FDG–PET series with PN [10]. We found a correlation between FDG uptake and change in PN volume over the subsequent year. Although this correlation is moderate within our study of 13 serially-evaluable patients, we also acknowledge that the sample size was modest. It is possible that with increased sample size, if the correlation estimate holds, it will become statistically significant. Furthermore, the analysis in Fig. 2 supports that a biologically based threshold effect exists and may be diagnostically useful in the clinical setting.

In the future, FDG–PET may provide valuable information to assess PN response to therapy. Because of the variability in growth rate of PN over time, it is often difficult to determine if tumor growth arrest is due to a therapeutic intervention or represents a spontaneous phenomenon which may be noted during the natural course of the disease. In addition, the traditional model of treatment response defined by tumor shrinkage is based on malignant disease. In benign lesions, persistent tumor after therapy does not always translate into inevitable progression. Surrogate markers of treatment response which address biological or functional changes in the tumor may have more prognostic significance. Studies of FDG–PET in a variety of solid tumors demonstrate its promising role in

the evaluation of treatment response [31–33]. Reductions in tumor FDG uptake have been detected prior to changes in tumor size and have been predictive of prolonged disease remission. We believe that FDG–PET may demonstrate similar efficacy in predicting early response to treatment for PN.

Conclusion

The majority of PN lesions have low FDG–PET SUV values, consistent with the benign nature of these lesions. Our data support the hypothesis that FDG–PET imaging predicts PN tumor growth in patients with NF1 and, therefore, may assist clinician decision making with regard to treatment of PN and enrollment in clinical trials.

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