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ORIGINAL RESEARCH ARTICLE

The utility of [^{18}F]FDG PET/CT in children with neurofibromatosis type 1: A retrospective single-center study

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ABSTRACT

Introduction: Neurofibromatosis type 1 (NF1) is a prevalent inherited condition, having a risk for malignant conversion to malignant peripheral nerve sheath tumor (MPNST). Our study objective was to assess the effectiveness of [^{18}F]FDG PET/CT and Magnetic Resonance Imaging (MR) in identifying early transformation in pediatric patients, given the limited data available in existing literature.

Methods: In this study children with suspected or confirmed NF1 who underwent [^{18}F]FDG between January 2007 and April 2024 were included in a retrospective cross-sectional analysis. Exclusion criteria was follow-up periods shorter than one-year post [^{18}F]FDG results.

Results: The study included 13 patients (6 females, 7 males), with a median age of 11 years, and a total of 16 lesions. Only two lesions were confirmed by biopsy to have undergone malignant transformation into a MPNST. Although the findings varied, [^{18}F]FDG imaging was able to anticipate the malignant transformation only in one of these two cases.

Conclusion: Due to the limited sample size, definitive conclusions could not be provided. We were unable to propose a specific SUVmax cutoff to predict the malignant transformation of neurofibromas in children with NF1 disease.

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INTRODUCTION

Neurofibromatosis type 1 (NF1) ranks among the most prevalent inherited disorders, estimated at 1 in 3,000 individuals. It manifests as a multisystem condition characterized by various clinical features, including café-au-lait spots, neurofibromas, optic gliomas, hamartomas, and bone dysplasia. Transformation into malignant peripheral nerve sheath tumor (MPNST) occurs in 2-5% of NF1 cases, with an overall incidence in the general population of 0.001% [1]. The lifetime risk of a subtype of neurofibroma called peripheral plexiform neurofibroma (PPN) which is typically larger, more diffuse and more prone to complications, transforming into MPNST stands at 10% [2]. Detection of MPNSTs proves challenging and is associated with a grim prognosis [3]. Hence, investigating and biopsy of painful and enlarging PPNs are advisable [4]. Management of such cases necessitates the involvement of multidisciplinary teams comprising clinicians and scientists with expertise in this disease's diagnosis and treatment [3].

Various imaging modalities, including [18F]FDG PET/CT, hold promise in discerning between malignant and benign neurofibromas. However, their efficacy in the pediatric population remains limited due to limited data [5]. Additionally, the correlation between MRI findings and [18F]FDG uptake remains poorly understood. The potential of [18F]FDG to predict malignant transformation of neurofibromas into MPNSTs raises the possibility of reducing the need for biopsies and surgical excisions.

METHODS

Study population

This is a retrospective cross-sectional study. Children with suspected or diagnosed NF1 who underwent an [18F]FDG PET/CT during the period of January 2007 to April 2024 are included. Patients with a follow-up period of less than 1 year after FDG results were excluded. Initially 17 patients were found to have [18F]FDG PET/CT and history of NF1. However, 4 were excluded due to the following reasons: a case with neurofibromatosis type 2 with schwannoma, a case with clinical suspicion of NF1 turned out to be Ewing sarcoma, a case of NF1 with rhabdomyosarcoma and [18F]FDG PET/CT done after 2 cycles of chemotherapy, and a case of NF1 with brain sarcoma and [18F]FDG PET/CT done post resection.

Study protocol

The included patients [18F]FDG PET/CT and MR images were retrieved on PACS and GE workstation and reviewed to consensus by two Nuclear medicine physicians and one expert radiologist. [18F]FDG PET/CT images were evaluated qualitatively and semi-quantitatively. We used liver background uptake as a reference; uptake in the lesion was considered positive if it had uptake similar or more than liver uptake. Regions of interest (ROIs) was drawn around each lesion and the maximum standardized uptake value (SUVmax), SUV normalized by lean body mass (SUVlbm), and SUV normalized by body surface area (SUVbsa) were calculated. For measuring the SUV of the lesions, 2-cm diameter ROIs were placed in two non-consecutive slices. We used an SUVmax cut off of 3.5 to call it malignant as it has been used in prior studies, SUVmax less than 2.0 considered likely benign, and in between as indeterminate [6, 7].

The MR images were reviewed and a panel of image-based criteria was used including: T1 and T2 heterogeneity, alteration or absence of target appearance, pattern of enhancement in post-gadolinium imaging, presence or absence of irregular margins, intralesional cystic changes and perilesional edema [8]. [18F]FDG PET/CT and MR Studies were then grouped into 3 categories: Likely benign, indeterminate and likely malignant. Time interval between [18F]FDG PET/CT and MR was registered. All available notes on clinical course of the disease, pathology of biopsies and surgically excised lesions were reviewed on electronic health records and then correlated with the results of [18F]FDG PET/CT and MR. The local ethics committee approved the study protocol.

[18F]FDG PET/CT protocol

Imaging was carried out on all patients after a 4-6 hour fast. At the time of [18F]FDG injection, all patients had fasting a blood glucose level of less than 11 mmol/L. Image acquisition was performed approximately 60 minutes after injection of 5.18 MBq/kg (0.14 mCi/kg) using a minimum dose of 37 MBq (1 mCi) up to a maximum of 370 MBq (10 mCi) for all patients. Imaging was acquired using either a Philips 16-MDCT PET/CT or GE Discovery MI cameras. The time of bed position was 5 min for 16-MDCT PET/CT hybrid scanner (Gemini GXL, Philips Healthcare) and 3 min for SiPM PET/CT (GE Discovery MI) scanner. The images were displayed as coronal, sagittal, and transaxial sections.

MRI protocol

1.5 Tesla superconducting system (Philips Gyroscan S15, Philips Medical Systems) was used for MR. Images were taken in the axial and coronal planes with a slice thickness of 5 mm and an interscan distance of 0.5 mm. Coronal STIR images (TR/TE 2000/25, TI 150) were performed and axial T1 images (TR/TE 700/20) were carried out before and after the administration of gadolinium glumine-triaminepentacetic acid contrast medium (0.2 ml/kg).

Statistical analysis

Due to small cohort number, simple statistical analysis was done using Excel (Microsoft, Redmond, USA).

RESULTS

Thirteen patients were included in the study, 6 females (46%) and 16 lesions. The results were heterogeneous with only two lesions biopsy-proved to be MPNST (Tables 1 and 2), from which one was [^{18}F]FDG positive (Figure 1).

[^{18}F]FDG PET/CT semi-quantitative assessment

SUVmax, SUVlbm and SUVbsa were calculated for each lesion. Of the lesions considered FDG-avid (n=13), ranges for SUVmax, SUVlbm and SUVbsa were 1.1-8.3, 0.8-6.2, and 0.4-2.3, respectively.

Table 1. Clinical features and pathology in 13 NF1 patients

No	Age (yr)	Sex	Pain	Increase in size	Neurologic deficit	Pathology
1	12	M	Yes	Yes	Yes	Neurofibroma
2	9	M	No	Yes	No	Neurofibroma
3	14	F	Yes	Yes	No	Neurofibroma
4	15	F	No	Yes	No	Neurofibroma
5	11	M	Yes	Yes	No	Neurofibroma
6	17	F	Yes	Yes	No	Neurofibroma (atypical)
7	16	M	No	Yes	No	NA
8	8	F	Yes	Yes	Yes	Neurofibroma
9	15	F	Yes	Yes	Yes	MPNST
10	7	F	No	Yes	No	Neurofibroma
11	10	M	Yes	Yes	Yes	Neurofibroma
12	7	M	No	Yes	No	NA
13	9	M	Yes	Yes	No	MPNST

NF1: Neurofibromatosis type 1, MPNST: Malignant peripheral nerve sheath tumor, NA: Not available, biopsy was not done as imaging features were not suspicious and has a stable appearance on follow-up for at least 1 year

Table 2. [^{18}F]FDG features and pathology of 13 NF1 patients with 16 lesions

No	Site	SUVmax	SUVlbm	SUVbsa	Nuclear Medicine Physician opinion	Pathology
1	R Foot	0.4	0.3	0.1	M-	Neurofibroma
2	L Axilla	3.3	3.02	1.3	IN	Neurofibroma
3	L Arm	8.3	6.16	2.3	M+	Neurofibroma
4	R Arm	4.4	3.4	1.3	M+	Neurofibroma
5	R Neck	1.9	1.8	0.7	M-	Neurofibroma
6	L Leg	3.5	2.5	0.9	IN	Neurofibroma (atypical)
	L Popliteal Fossa	3.5	2.4	0.9	IN	NA
	L Thigh	3.8	2.7	1	M+	Neurofibroma
7	L Neck	2.12	1.8	0.65	M-	NA
8	L Neck	1.5	1.16	0.5	M-	NA
	L Thigh	3.9	3.07	1.33	M+	NA
9	R Thigh	2	1.2	0.44	M-	MPNST
10	R Leg	1.1	0.8	0.4	M-	Neurofibroma
11	Pelvis	2.2	1.01	0.39	M-	Neurofibroma
12	Pelvis	0.7	0.6	0.3	M-	NA
13	R Supraclavicular	4.8	4.32	1.71	M+	MPNST

L: Left, R: Right, NF1: Neurofibromatosis type 1, IN: Indeterminate), M-: Likely benign, M+: Likely malignant, NA: Not available, MPNST: Malignant peripheral nerve sheath tumor, SUVmax: Maximum standardized uptake valuem SUVlbm: Standardized uptake value normalized by lean body mass, SUVbsa: Standardized uptake value normalized by body surface area

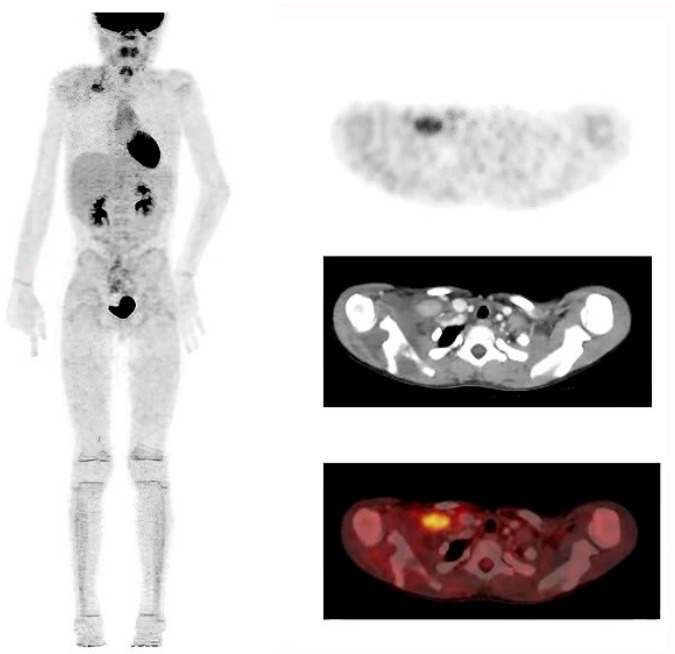

Figure 1. An [18F]FDG-avid heterogeneous lesion corresponding to plexiform neurofibromatosis in the right supraclavicular region (SUVmax= 4.8), considered PET positive, confirmed by pathology as malignant peripheral nerve sheath tumor

MR assessment

One out of the 16 lesions seen on [18F]FDG PET/CT has no available MR correlation. The time interval between [18F]FDG PET/CT and MR was 1-11 months. The range of maximal dimension of the lesions in mm was 18-110 mm. On T1-weighted images, 11 lesions showed homogenous signal pattern while 4 lesions showed heterogeneous signal pattern. On T2-weighted images, 5 lesions showed homogenous signal pattern while 10 lesions showed heterogeneous signal pattern. Target appearance was present in 6 lesions, altered in 4 lesions and absent in 5 lesions. Post Gadolinium contrast enhancement pattern was homogenous in 3 lesions, heterogeneous in 7 lesions, peripheral in 4 lesions and absent in one lesion. Perilesional edema was present in 3 lesions and absent in 12 lesions. Intralesional cystic changes was absent in all 15 lesions. Five lesions had irregular margins and 10 lesions had smooth margins. Unfortunately, DWI weighted images were not available in all patients and has not been included in the analysis (Table 3). The interpretation of PET and MRI regarding benign or malignant status of lesions, along with final pathology results are summarized in Table 4.

DISCUSSION

Our findings in this small patient cohort failed to establish a clear correlation between [18F]FDG PET/CT and MR findings and the final pathology report in most cases. With only two biopsy-confirmed malignancies in our study, reaching definitive conclusions proved challenging. Notably, one case diagnosed pathologically as atypical neurofibroma was deemed indeterminate on [18F]FDG PET/CT and likely benign on MR. Among the four lesions described as likely malignant on MR, three were interpreted as likely benign and one as likely malignant on [18F]FDG PET/CT (Table 4).

Reviewing existing literature reveals that most studies on the use of [18F]FDG PET/CT to detect early malignant transformation of neurofibroma to MPNST have been conducted on adult patients. MRI is typically employed to assess the site and extent of the disease, while [18F]FDG PET/CT evaluates metabolic activity [9]. In one paper, they reported a specificity of 90% and a sensitivity of 61% in the presence of two of the following MR features in predicting early malignant transformation of PPN: large tumor dimension, perilesional edema, peripheral enhancement, and intratumoral cystic changes [8].

Some papers suggested acquiring delayed images and prolonging uptake time up to 200 minutes after [18F]FDG injection to increase specificity [9]. Multiple studies in adult population suggested a SUVmax cut-off to call a lesion suspicious for malignant transformation. In one study, they proposed a SUVmax cut-off of 4.0 that has a high sensitivity and specificity of 1.0 and 0.94, respectively [10].

Table 3. MR features and pathology of 13 NF1 patients with 16 lesions

No	Site	Size (mm)	T1	T2	Target appearance	Enhancement pattern	Perilesional edema	Intratumoral cystic changes	Margin	Radiologist opinion	Pathology
1	R Foot	39	HM	HT	A	HT	PR	A	I	M+	Neurofibroma
2	L Axilla	31	HM	HM	A	HM	A	A	I	IN	Neurofibroma
3	L Arm	51	HT	HT	AL	P	A	A	S	IN	Neurofibroma
4	R Arm	51	HM	HM	A	P	A	A	S	M+	Neurofibroma
5	R Neck	39	HM	HT	AL	HT	A	A	S	IN	Neurofibroma
6	L Leg	47	HM	HM	PR	P	A	A	S	M-	Neurofibroma (atypical)
	L Popliteal Fossa	35	HM	HM	PR	HT	A	A	S	M-	NA
	L Thigh	18	HM	HT	AL	HT	A	A	S	IN	Neurofibroma
7	L Neck	109	HT	HT	AL	HT	A	A	S	M-	NA
8	L Neck	60	HM	HM	PR	HM	A	A	I	M-	NA
	L Thigh	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
9	R Thigh	180	HT	HT	A	HT	PR	A	S	M+	MPNST
10	R Leg	32	HM	HT	A	P	PR	A	I	M+	Neurofibroma
11	Pelvis	110	HT	HT	PR	HT	A	A	S	M-	Neurofibroma
12	Pelvis	56	HM	HT	PR	N	A	A	I	M-	NA
13	R Supraclavicular	43	HM	HT	PR	HM	A	A	S	M-	MPNST

L: Left, R: Right, A: Absent, AL: Altered, I: Irregular; HM: Homogenous, HT: Heterogeneous; N: No enhancement, P: Peripheral; PR: Present, S: Smooth; NA: Not available, IN: Indeterminate, M-: Likely benign, M+: Likely malignant, MR: Magnetic resonance imaging, NF1: Neurofibromatosis type 1, MPNST: Malignant peripheral nerve sheath tumor

Table 4. [18F]FDG and MR features along with final pathology of 13 NF1 patients with 16 lesions

No	Site	[18F]FDG-MR interval (months)	FDG opinion	MR opinion	Pathology
1	R Foot	5	M-	M+	Neurofibroma
2	L Axilla	1	IN	IN	Neurofibroma
3	L Arm	1	M+	IN	Neurofibroma
4	R Arm	4	M+	M+	Neurofibroma
5	R Neck	1	M-	IN	Neurofibroma
6	L Leg	1	IN	M-	Neurofibroma (atypical)
	L Popliteal Fossa	1	IN	M-	NA
	L Thigh	1	M+	IN	Neurofibroma
7	L Neck	1	M-	M-	NA
8	L Neck	10	M-	M-	NA
	L Thigh	N	M+	NA	NA
9	R Thigh	1	M-	M+	MPNST
10	R Leg	1	M-	M+	Neurofibroma
11	Pelvis	1	M-	M-	Neurofibroma
12	Pelvis	4	M-	M-	NA
13	R Supraclavicular	1	M+	M-	MPNST

L: Left, R: Right, IN: Indeterminate, M-: Likely benign, M+: Likely malignant, N: No available MR correlation, NA: Not available, MR: Magnetic resonance imaging, MPNST: Malignant peripheral nerve sheath tumor

A SUVmax cut-off ≥ 6.1 had a sensitivity of 94% and a specificity of 91% in another study [11]. In one paper, they described that all lesions with SUVmax <4.3 were benign and >8.1 were malignant [12]. No malignant lesions were found with SUVmax ≤ 3.15 in another study [13]. Another [18F]FDG parameter that was described in the literature was intra-tumoral uptake heterogeneity, where it showed significant correlation with the detection of malignant transformation based on Salamon et al's. study [14]. Tumor-to-liver ratio has been described as another parameter to detect malignant transformation in pre-existing PPN with a cut-off of >2.6. Both SUVmax and tumor-to-liver ratio had a sensitivity of 100%, but the ratio had a higher specificity [15]. In one paper, they reported [18F]FDG SUVmax sensitivity of 95% and specificity of 72% for MPNST and suggested that specificity could be improved using concurrent other PET tracer like [11C]C-methionine [16]. Multiple studies suggested that [18F]FDG is useful in detecting early malignant transformation of neurofibroma to MPNST [3, 6, 9, 17]. It has been reported that tumor SUV was a significant parameter for prediction of survival in NF1 patients with MPNSTs, while pathological tumor grading did not predict outcome [18]. Fewer studies were done on pediatric population, one showed [18F]FDG to be useful in detecting early malignant transformation but they don't support it as screening tool in majority of patients and suggested to be used as an adjunct to MRI [5, 10, 12]. A study by Geitenbeek et al. showed that [18F]FDG provides sufficient accuracy for detecting MPNSTs in pediatric. While SUV values in pediatric MPNSTs may be lower, the tumor-to-liver ratios remain unchanged [19].

Yue X et al. assessed PET imaging of NF1 using L-[18F]FETrp radiotracer and compared the results to those obtained with commercial [18F]FDG. They found that L-[18F]FETrp provided higher tumor-to-brain SUV ratios than [18F]FDG. Additionally, this tracer demonstrated stability with minimal in vivo defluorination. The authors concluded that L-[18F]FETrp could be a promising radiotracer for guiding MPNST surgery and evaluating treatment responses [20].

Finally, it has been recommended that these patients require careful longitudinal clinical and imaging monitoring [21].

Overall, few studies have focused on the pediatric population, with some indicating [18F]FDG's utility in detecting early malignant transformation but cautioning against its routine use as a screening tool. It has been recommended to utilize [18F]FDG PET/CT as an adjunct to MRI in cases where there is clinical suspicion of malignant transformation of PPN to MPNST. Longitudinal clinical and imaging monitoring is deemed essential for these patients.

Limitation

One of the limitations of our study include its small sample size, which limits its generalizability to a broader population. Additionally, being a single-site clinical experience may introduce bias.

CONCLUSION

[^{18}F]FDG PET/CT or MR alone may not be an accurate method to predict malignant degeneration in pediatric NF1. Due to the small sample size and heterogeneous results, it was not possible to determine a definitive SUVmax cut-off to predict malignant transformation of PPN to MPNST in pediatric NF1 patients. A larger cohort study is warranted to ascertain whether [^{18}F]FDG PET/CT should complement MR imaging in pediatric NF1 patients with suspected malignant transformation to MPNST.

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