The role of ^{18}F-FDG PET/CT in the evaluation of pediatric transplant patients

Jigang Yang[1,2] MD, PhD,
Hongming Zhuang[2] MD, PhD

1. Department of Nuclear Medicine, Beijing Friendship Hospital affiliated to Capital Medical University, Beijing 100050, PR China
2. Department of Radiology, The Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA

Keywords: PET/CT
- Pediatric transplantation
- Post transplant disease
- Lymphoproliferative disorder
- Fever of unknown origin

Correspondence address:
Jigang Yang MD, PhD
Address: 95 Yong An road,
Xi Cheng District,
Beijing, China, 100050.
13681221974@163.com

Received:
15 March 2015
Accepted revised:
20 May 2015

Abstract

Objective: Intensive immunosuppressive regimens effectively reduce acute or chronic rejection in transplant patients, while these regimens can result in long term side-effects such as viral infection, fever, secondary tumor(s) et al. Our aim was to evaluate the role of 18-fluoro-2-deoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in pediatric transplant patients. **Subjects and Methods**: Forty one ^{18}F-FDG PET/CT scans in 18 patients before or after transplant were analyzed retrospectively. One patient had PET/CT scan prior to transplantation. Seventeen patients had PET/CT scan(s) following transplantation. The PET/CT scan was used to evaluate the therapy response of post transplant lymphoproliferative disorder (PTLD) in 11 patients, establish the cause of fever of unknown origin (FUO) in 5 patients, and restage in 2 patients. **Results**: PET/CT scan showed development in 3 PTLD patients, improvement in 4 PTLD patients, development and improvement in 1 PTLD patient, new lesions in 1 PTLD patient, and no lesions in 2 PTLD patients. The scan demonstrated the cause of FUO in 2 patients but did not demonstrate the cause of FUO in 2 patients. The PET/CT was false positive in 1 FUO patient and did not show any new lesions in 2 restaging patients. **Conclusion**: PET/CT may have an important role in follow-up of pediatric transplant patients. Further investigations with more patients are necessary to assess the validity of our findings.

Hell J Nucl Med 2015; 18(2): 136-139 *Epub ahead of print: 19 July 2015* *Published online: 5 August 2015*

Introduction

Transplantation (including soft tissue organ transplantation and bone marrow transplantation) is being used increasingly as treatment for children with end-stage organ diseases, hematopoietic rescue from therapy used to treat malignancies, and cure for primary immune deficiencies [1]. The numbers of transplantation procedures performed on children is substantially less than those performed on adults, with recipients under the age of 18 years accounting for only 7.7% of all solid organ transplantations performed in the United States [2]. The success of transplantation can be attributed to several factors including advances in surgical procedures and organ preservation techniques, improved immunosuppressive and antiviral regimens, and changes in donor organ allocation [3]. It is essential that pediatric post-transplantation patients maintain a good quality life, free of significant long term side-effects. Intensive immunosuppressive regimens effectively reduce acute or chronic rejection, while they can result in long term side-effects such as viral infection, fever, secondary tumor etc [4]. Combined 18-fluoro-2-deoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) scan has high resolution and diagnostic accuracy, allows imaging to be performed quickly and correlates anatomic location with function [5]. The ^{18}F-FDG PET/CT scan has been widely used in the diagnosis of pediatric malignancy [6] and in some benign processes [7, 8]. In this article, we evaluate the role of ^{18}F-FDG PET/CT in the follow-up of pediatric transplant patients.

Subjects and Methods

Patients

Forty one ^{18}F-FDG PET/CT scans in 18 patients (10 females, 8 males, ages between 2 and 18 years) prior to or following transplantation were analyzed retrospectively. Nine patients had only one ^{18}F-FDG PET/CT scan. Nine patients had more than one ^{18}F-FDG PET/CT scan. One patient had another ^{18}F-FDG PET/CT scan before transplantation. Seventeen patients had ^{18}F-FDG PET/CT scans after transplantation. The transplantation pro-

cedure included bone marrow, liver, heart, renal and lung transplantation. Five patients had liver transplantation, four patients with bone marrow transplantation, four with heart transplantation, three with renal transplantation, and two with lung transplantation. The ^{18}F-FDG PET/CT scan was used to evaluate the therapy response of post transplant lymphoproliferative disorder (PTLD) in 11 patients, detect the cause of FUO in 5 patients, and restage in 2 patients. All FUO patients had the ^{18}F-FDG PET/CT scan when the first-line diagnostic methods did not find abnormalities, or when the cause of FUO was unclear. First-line examinations including routine laboratory tests and conventional imaging methods were performed in all of these patients. Eight patients with PTLD had more than one ^{18}F-FDG PET/CT scan. Three patients with PTLD had only one ^{18}F-FDG PET/CT scan (Table 1).

^{18}F-FDG PET/CT image acquisition

All patients were required to fast for at least 4h prior to the study and limitation of physical activity was recommended. Serum glucose levels were measured before imaging and were below the threshold value of 7.8mmol/L (or 140mg/dL) at the time of radiotracer injection (5.18MBq/kg or 0.14mCi/kg of ^{18}F-FDG). Patients were kept in a warm, dark, quiet room after ^{18}F-FDG injection; 60mins later, whole-body PET emission images were obtained using a standard imaging protocol with subsequent image reconstruction with and without attenuation correction. Simultaneous CT scans of the same regions were performed without oral or intravenous contrast administration. All ^{18}F-FDG PET/CT scans were performed on a dedicated ^{18}F-FDG PET/CT scanner (Gemini, Philips Medical Systems, Bothell, WA, USA). Transverse, sagittal, and coronal PET and CT images were reconstructed and examined by experienced nuclear medicine physicians by visual and semiquantitative evaluation.

Results

Based on the pathological result, PTLD was diagnosed in 11 patients (patient 6 to 16). After the diagnosis of PTLD, 8 of 11 patients received related therapy and had ^{18}F-FDG PET/CT scan to monitor the therapy response. Based on ^{18}F-FDG PET/CT results, we classified the therapy response as development, improvement, mixed response including development and improvement. Three of 11 patients had only one ^{18}F-FDG PET/CT scan before therapy to staging the disease. The scan showed development in 3 PTLD patients (patients 6, 8 and 10) with more than one ^{18}F-FDG PET/CT scan and improvement in 4 PTLD patients (patient 7, 11,13 and 14) (Figure 1) with more than one ^{18}F-FDG PET/CT scan. In patient 15, the ^{18}F-FDG PET/CT showed some mixed metabolic response compared with the prior study. There was an overall increase in size area and the degree of ^{18}F-FDG uptake within some lesions, interval decrease in size but increase in ^{18}F-FDG uptake in other lesions, and interval decrease in ^{18}F-FDG uptake within some lesions in this patient. We classified this ^{18}F-FDG PET/CT result as a mixed response. The ^{18}F-FDG PET/CT results of 8 of 11 patients influenced the further management of PTLD. There were new lesions in one PTLD patient and no lesions in two PTLD patients based on only one scan.

The cause of FUO was demonstrated by the scan in two patients. The scan of patient 2 showed hypermetabolic soft tissues in the lateral aspect of right greater trochanter and right inner pelvic wall, which was confirmed as staphylococcus epidermitis. The scan of patient 5 before liver transplantation showed abnormal, focal increased ^{18}F-FDG uptake in the lateral segment of the left lobe of the liver, which was confirmed as cholangiitis by biopsy. The ^{18}F-FDG PET/CT scan did not demonstrate the cause of FUO in 2 patients. Further examinations still did not detect the cause of FUO in these 2 patients. Patient 4 was a 6 years old male with FUO and renal transplantation history and the scan showed increased ^{18}F-FDG activity in the transplanted kidney with a photopenic region in the renal pelvis, which indicated that the renal cortical activity was not from radioactive urine. Instead, the renal activity was more likely the cause of the FUO. However, further examination did not confirm the increased ^{18}F-FDG uptake in the transplanted kidney as the cause of FUO. We classified the result as a false positive. The scan did not show any new lesions in 2 restaging patients. One patient (patient 17) with Hodgkin's lymphoma and bone marrow transplantation had the ^{18}F-FDG PET/CT scan to restage the disease, which did not show evidence of active hypermetabolic disease. The other patient (patient 18) with renal Wilm's tumor and lung transplantation for lung metastasis also had the scan to restage the disease, which did not show evidence of hypermetabolic malignancy (Table 1).

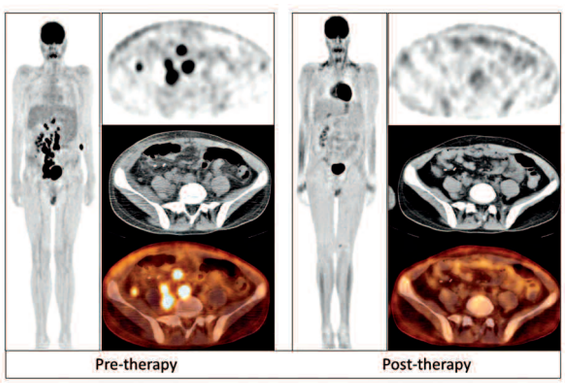

Figure 1. A 12 years old girl was diagnosed as post-transplant lymphoproliferative disorder post heart transplantation. The ^{18F}-FDG PET/CT of pre-therapy showed multiple foci of ^{18F}F-FDG accumulation in the retroperitoneal region. The ^{18F}F-FDG PET/CT of post-therapy did not show abnormal ^{18F}F-FDG accumulation. Based on these ^{18F}F-FDG PET/CT results, we classified the therapy response as improvement.

Discussion

The clinical outcomes of transplantations are directly related to the transplanted organ (acute or chronic allograft rejection) and those that are caused by post transplant therapies (fever, infection, malignancy). Many of the diseases experienced in patients with long term allograft survival are associated with the immunosuppressive regimens to which the success of the

transplant organ is attributed [3]. Pediatric patients still remain one of the highest risk groups for cancer post transplant. The relative risk of cancer among transplanted pediatric patients is about two to three times higher than in the general population [9,10]. Penn et al. (1994) reported that the incidence of malignancy among pediatric transplant recipients was as high as 10 times the incidence for the same age group [11]. North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) reported that the incidence of malignancy in pediatric renal transplant recipients was 2.4%. The male to female ratio in pediatric transplantation recipients with cancer was lower than in adult patients, at 1.2: 1 [12]. Among pediatric solid organ transplant recipients, PTLD remains the most common neoplasm, affecting between 1% and 10% of all patients based on the transplanted organ. Israel Penn Transplant Tumor Registry reported that over 50% of pediatric transplant malignancies were PTLD [13]. Post transplant LD is a serious, life threatening complication of solid organ transplantation and bone marrow transplantation leading to high mortality. The reported incidence of PTLD is very variable as is its related mortality (30%-60%) [14]. Post transplanted LD represents a heterogeneous group of lymphoproliferative diseases, ranging from Epstein-Barr virus (EBV) associated polyclonal proliferation to highly aggressive monomorphic proliferations, such as diffuse large B-cell lymphoma [15]. There is no consensus about the optimal treatment of PTLD. It is generally agreed that three major strategies should be applied: restoration of the recipient' immunity (to limit the EBV infection), elimination of EBV and removal of neoplastic B cells [16]. Previous studies have reported the role of ^{18}F-FDG PET/CT in the evaluation and follow-up of adult PTLD [17].

In our study, 8 of 11 patients had ^{18}F-FDG PET/CT scans to monitor the therapy response after related therapy. The therapy response included development in 3 patients, improvement in 4 patients and mixed response in 1 patient. The scan results of these 8 patients influenced the further management of PTLD. Three of 11 patients had only one ^{18}F-FDG PET/CT scan before therapy to staging the disease.

Fever of unknown origin was defined as recurrent fever of 38,3°C or higher, lasting 2-3 weeks or longer, and not determined after 1 week of hospital evaluation [18]. Durak et al. (2007) offered new definition for different subsets of populations with FUO as following: classic FUO, nosocomial FUO, neutropenic FUO, and HIV associated FUO. Unfortunately, transplant patients were not included [19]. The precise incidence of fever in different transplant patients is not well known. In a prospective evaluation of the cause of fever in liver transplant recipients, Chang et al. (1998) reported that fever was caused by infection in 78% patients and was non-infectious in 22% [20]. In our study, 5 patients had ^{18}F-FDG PET/CT scans to locate the etiology of the FUO, and in 2 of these 5 FUO patients it was located. Seshadri et al. (2012) evaluated the accuracy of the ^{18}F-FDG PET/CT scan in patients with FUO. They reported that the overall sensitivity, specificity, positive predictive value and negative predictive value of ^{18}F-FDG PET/CT were 86%, 78%, 86% and 78%, which were significantly higher than those of In-111 labelled leucocyte scintigraphy [21]. However, Sheng et al. (2011) reported that the specificity of ^{18}F-FDG PET/CT for detecting the cause of FUO was 33% [22]. In our study, the scan result of 1 patient was falsely positive. False positive ^{18}F-FDG PET/CT result was responsible for the poor specificity. The causes of a high false positive ^{18}F-FDG PET/CT may be that: a) the high rate of false positive is inevitable because the causes of FUO are obscure in a number of patients [23,24]; b) when the additional methods fail to locate the cause of FUO, it is probably reasonable to consider the abnormality as a false positive result; c) it is also difficult to differentiate physiologic uptake from pathologic uptake of ^{18}F-FDG, which causes variation in the number of positive results [22].

In our study, ^{18}F-FDG PET/CT scan in 2 of 5 patients did not

Table 1. *Table 1 clinical and PET/CT information of all patients*

Patient No	Age/G	Times PET/CT	Result	Cause and transplant	Evaluation
1	7/m	1	positive	FUO after BM tranplant	no lesion
2	16/f	4	»	FUO after BM tranplant	positive
3	2/m	1	negative	FUO after liver transplant	no lesion
4	6/m	1	positive	FUO after renal transplant	false positive
5	18/f	1	»	FUO pre liver transplant	positive
6	10/f	8	»	PTLD after heart transplant	development
7	15/f	3	»	PTLD after heart transplant	improvement
8	7/m	1	»	PTLD after liver transplant	development
9	11/f	1	negative	PTLD after renal transplant	no lesion
10	18/f	5	positive	PTLD post BM transplant	development
11	12/f	2	»	PTLD post heart transplant	improvement
12	18/m	1	»	PTLD post heart transplant	new lesion
13	5/f	2	negative	PTLD post liver transplant	improvement
14	18/m	3	positive	PTLD post liver transplant	improvement
15	18/m	3	»	PTLD post lung transplant	mixed
16	10/f	1	negative	PTLD post renal transplant	no lesion
17	15/m	2	»	staging, post BM transplant	no lesion
18	18/f	1	»	staging, post lung transplant	no lesion

FUO: fever of unknown origin; PTLD: post transplantation lymphoproliferative disorder; f: female; m: male; BM: bone marrow

show the cause of FUO. Further examination did not locate the cause of FUO in 2 patients with negative ^{18}F-FDG PET/CT scan. We classified this result as a true negative. Balink H et al. (2009) reported high negative predictive value of ^{18}F-FDG PET/CT for assessment of FUO. This scan allows exclusion of a focal etiology of FUO with a high degree of certainty. When systemic diseases were excluded by other diagnostic tests, a negative ^{18}F-FDG PET/CT scan, in combination with negative first-level diagnostic methods may avoid the need for further futile investigations [25, 26]. Up to now the ^{18}F-FDG PET/CT scan is still not a routine procedure in the management of transplant patients due to high cost and limited availability. Based on our study, the ^{18}F-FDG PET/CT scans have an important role in management and follow-up of pediatric transplant patients.

The limitations of this study need to be considered. It is a retrospective study with a small sample size and a heterogeneous patient population.

In conclusion, the ^{18}F-FDG PET/CT scan may have an important role in management and follow-up of pediatric transplant patients. Further investigations with more patients are necessary to assess the validity of our findings.

Acknowledgements

Jigang Yang was partially supported by the Beijing Natural Science Foundation (no. 7152041), and by the Beijing Health technical personnel training plan (no. 2013-3-066).

The authors declare that they have no conflicts of interest.

Bibliography

1. Michaels MG, Green M. Infections in pediatric transplant recipients: not just small adults. *Hematol Oncol Clin North Am* 2011; 25: 139-50.
2. Michaels MG, Green M. Infections in pediatric transplant recipients: not just small adults. *Infect Dis Clin North Am* 2010; 24: 307-18.
3. LaRosa C, Baluarte HJ, Meyers KE. Outcomes in pediatric solid organ transplantation. *Pediatr Transplant* 2011; 15: 128-41.
4. Kelly DA. Current issues in pediatric transplantation. *Pediatr Transplant* 2006; 10: 712-20.
5. Bleeker-Rovers CP, Vos FJ, de Kleijn EM et al. A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol. *Medicine (Baltimore)* 2007; 86: 26-38.
6. Makis W, Ciarallo A, Novales-Diaz JA et al. Progressive transformation of germinal centers in a pediatric patient: initial evaluation and follow-up with serial F-18 FDG PET/CT imaging. *Clin Nucl Med*; 36: e139-41.
7. Yang J, Codreanu I, Servaes S et al. Earlier Detection of Bone Metastases From Pleomorphic Liposarcoma in a Pediatric Patient by FDG PET/CT Than Planar ^{99m}Tc MDP Bone Scan. *Clin Nucl Med* 2012; 37: e104-7.
8. Rosenbaum J, Basu S, Beckerman S et al. Evaluation of diagnostic performance of ^{18}F-FDG-PET compared to CT in detecting potential causes of fever of unknown origin in an academic centre. *Hell J Nucl Med* 2011;14: 255-9.
9. Wilde GE, Moore DJ, Bellah RD. Posttransplantation lymphoproliferative disorder in pediatric recipients of solid organ transplants: timing and location of disease. *Am J Roentgenol* 2005; 185: 1335-41.
10. Bartosh SM, Leverson G, Robillard D, et al. Long-term outcomes in pediatric renal transplant recipients who survive into adulthood. *Transplantation* 2003; 76: 1195-200.
11. Penn I. De novo malignancy in pediatric organ transplant recipients. *J Pediatr Surg* 1994; 29: 221-6; discussion 227-8.
12. Shroff R, Rees L. The post-transplant lymphoproliferative disorder-a literature review. *Pediatr Nephrol* 2004; 19: 369-77.
13. Buell JF, Gross TG, Thomas MJ et al. Malignancy in pediatric transplant recipients. *Semin Pediatr Surg* 2006; 15: 179-87.
14. Mucha K, Foroncewicz B, Ziarkiewicz-Wroblewska B et al. Post-transplant lymphoproliferative disorder in view of the new WHO classification: a more rational approach to a protean disease? *Nephrol Dial Transplant* 2010; 25: 2089-98.
15. Tanner JE, Alfieri C. The Epstein-Barr virus and post-transplant lymphoproliferative disease: interplay of immunosuppression, EBV, and the immune system in disease pathogenesis. *Transpl Infect Dis* 2001; 3: 60-69
16. Everly MJ, Bloom RD, Tsai DE et al. Posttransplant lymphoproliferative disorder. *Ann Pharmacother* 2007; 41: 1850-8.
17. Makis W, Lisbona R, Derbekyan V. Hodgkin lymphoma post transplant lymphoproliferative disorder following pediatric renal transplant: serial imaging with F-18 FDG PET/CT. *Clin Nucl Med* 2010; 35: 704-5.
18. Petersdorf RG. Fever of unknown origin. An old friend revisited. *Arch Intern Med* 1992; 152: 21-2.
19. Bouza E, Loeches B, Munoz P. Fever of unknown origin in solid organ transplant recipients. *Infect Dis Clin North Am* 2007; 21: 1033-54, ix-x
20. Chang FY, Singh N, Gayowski T et al. Fever in liver transplant recipients: changing spectrum of etiologic agents. *Clin Infect Dis* 1998; 26: 59-65.
21. Seshadri N, Sonoda LI, Lever AM et al. Superiority of (18)F-FDG PET compared to (111) In-labelled leucocyte scintigraphy in the evaluation of fever of unknown origin. *J Infect* 2012; 65: 71-79.
22. Sheng JF, Sheng ZK, Shen XM et al. Diagnostic value of fluorine-18 fluorodeoxyglucose positron emission tomography/computed to mography in patients with fever of unknown origin. *Eur J Intern Med* 2011; 22: 112-6.
23. Meller J, Sahlmann CO, Scheel AK. ^{18}F-FDG PET and PET/CT in fever of unknown origin. *J Nucl Med* 2007; 48: 35-45.
24. Hao R, Yuan L, Kan Y et al. Diagnostic performance of ^{18}F-FDG PET/CT in patients with fever of unknown origin: a meta-analysis. *Nucl Med Commun* 2013; 34: 682-8.
25. Balink H, Collins J, Bruyn GA et al. F-18 FDG PET/CT in the diagnosis of fever of unknown origin. *Clin Nucl Med* 2009; 34: 862-8.
26. Bleeker-Rovers CP, Vos FJ, Mudde AH et al. A prospective multicentre study of the value of FDG-PET as part of a structured diagnostic protocol in patients with fever of unknown origin. *Eur J Nucl Med Mol Imaging* 2007; 34: 694-703.