ORIGINAL ARTICLE
IN PULMONARY MEDICINE

Role and sensitivity of Positron Emission Tomography with [^{18}F] Fluorodeoxyglucose in diagnosis and follow-up of patients affected by chronic pulmonary aspergillosis (CPA)

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Abstract

Introduction: PET/CT is considered as a powerful tool to diagnose, stage, and monitor patients with a variety of diseases. In this study, we assessed the sensitivity and the degree of agreement between 18F-FDG PET/CT and serological tests in diagnosis and follow-up of patients affected by chronic pulmonary aspergillosis (CPA).
Methods: Thirty-seven adult patients (21 males and 16 females) affected by CPA were recruited during the study period (2010 - 2017). At the time of first diagnosis, we compared sensitivity of 18F-FDG PET/CT and serologic tests (i.e., identification of Aspergillus-specific IgE and IgG antibodies using IFA and ELISA). 12 months after the treatment, we repeated tests only in patients with possible active disease to make a comparison between serological tests and 18F-FDG PET/CT. Sensitivity was calculated as the proportion of positive results obtained with the index test among cases. The agreement between diagnostic techniques was assessed using the Kappa coefficient. The level of significance was set at 5% ($P < 0.05$).
Results: At the time of first diagnosis, agreement between 18F-FDG PET/CT and serologic tests was 'almost perfect' (88%, Kappa = 0.846, $P < 0.05$), whereas it was 'good' at 12 months follow-up (81%, Kappa = 0.684, $P < 0.05$). At first diagnosis, serological test had a higher sensitivity (94.59%, 95% Confidence Interval [CI] 81.81% to 99.34%) in comparison with 18F-FDG PET/CT (83.78%, 95% CI 67.99% to 93.81%). Conversely, at 12-month follow-up, 18F-FDG PET/CT showed higher sensitivity (93.75, 95% CI 69.77% to 99.84%) than serological test group (75%, 95% CI 47.62% to 92.73%).
Discussion and Conclusion: Our findings demonstrate that both methods are suitable and have almost equivalent sensitivity in diagnosis and follow-up of patients affected by CPA with active disease. 18F-FDG PET/CT scan is a reliable support tool for clinical and serological data in the diagnosis and follow-up of aspergillosis infection, providing additional information on metabolic activity, accurate anatomic localization and extent of disease.

KEY WORDS: Diagnosis; pulmonary aspergillosis; Positron Emission Tomography; sensitivity; serological tests.

Riassunto

Introduzione: La PET TC è considerata un potente strumento per la diagnosi, la stadiazione ed il monitoraggio di pazienti affetti da diverse patologie. In questo studio, abbiamo valutato la sensibilità ed il grado di accordo tra la PET TC con 18F-FDG e gli esami sierologici per la diagnosi ed il follow-up di pazienti affetti da aspergillosi polmonare cronica (APC).
Metodi: 37 pazienti adulti (21 di sesso maschile e 16 di sesso femminile) affetti da aspergillosi polmonare cronica sono stati recrutati durante il periodo di studio (2010 - 2017). Al momento della prima diagnosi, abbiamo confrontato la sensibilità della PET/TC con 18F-FDG con la sensibilità degli esami sierologici (ovvero anticorpi IgE ed IgG specifici anti-Aspergillus con metodo ELISA o IFA). Dodici mesi dopo il trattamento, abbiamo ripetuto i test solo nei pazienti con possibile malattia in fase di attività per fare un confronto tra gli esami sierologici e la PET TC con 18F-FDG. La sensibilità diagnostica è stata calcolata come la proporzione di positivi ottenuta tra i casi di malattia. L'accordo tra le tecniche diagnostiche è stata valutato usando il coefficiente Kappa. Il livello di significatività statistica è stato fissato a $P < 0.05$.
Risultati: Al momento della prima diagnosi, l'accordo tra la PET TC con 18F-FDG e gli esami sierologici è stato "quasi perfetto" (88%, Kappa = 0.846, $P < 0.05$), mentre è stato "buono" al follow-up dopo 12 mesi (81%, Kappa = 0.684, P < 0.05). Alla prima diagnosi, gli esami sierologici hanno riportato una sensibilità maggiore (94.59%, Intervallo Confidenziale [IC] al 95% 81.81% – 99.34%) rispetto alla PET TC con 18F-FDG (83.78%, IC 95% 67.99% – 93.81%). Al follow-up di 12 mesi, la PET TC con 18F-FDG ha evidenziato una sensibilità maggiore (93.75%, IC 95% 69.77% – 99.84%) rispetto agli esami sierologici (75%, IC 95% 47.62% – 92.73%).
Discussione e Conclusioni: I nostri risultati dimostrano che entrambi i metodi sono adeguati ed hanno una sensibilità quasi equivalente nella diagnosi e nel follow-up dei pazienti affetti da APC in fase di attività. La PET TC con 18F-FDG è uno strumento di supporto affidabile per i dati clinici e sierologici nella diagnosi e nel follow-up dell'infezione aspergillare, fornendo informazioni aggiuntive sull'attività metabolica, l'accurata localizzazione anatomica e l'estensione della malattia.

TAKE-HOME MESSAGE

^{18}F-FDG PET/CT scan is a reliable support tool for clinical and serological data in the diagnosis and follow-up of chronic pulmonary aspergillosis.

Competing interests - none declared.

Cite this article as: Schiraldi GF, Popescu CE, Chiericozzi M, Lo Cicero S, Allegri F, Mosca F, Rossetti C. Role and sensitivity of of Positron Emission Tomography with [18F]Fluorodeoxyglucose in diagnosis and follow-up of patients affected by chronic pulmonary aspergillosis (CPA). J Health Soc Sci. 2018;3(1):49-58

DOI 10.19204/2018/rlnd5

Received: 08/11/2017 Accepted: 02/03/2018 Published: 15/03/2018

INTRODUCTION

Chronic pulmonary aspergillosis (CPA) is a long-term infection of the lower respiratory tract caused by Aspergillus species (*A. fumigatus* is the most common species followed by *Aspergillus niger* and *Aspergillus flavus)* in patients with no severe chronic immune alterations.

The classification of CPA, introduced in 2003 has simplified the previous nosologic fragmentation [1–2]. This new, simplified classification system encompassing all pulmonary *Aspergillus* spp. infections includes three entities: (1) simple aspergilloma; (2) 'chronic cavitary pulmonary aspergillosis' (CCPA), as symptomatic complex aspergilloma or slowly progressive chronic necrotising pulmonary aspergillosis (CNPA) (> 3 months in duration), occurring in patients with a previous history of bronchopulmonary disease, with pre-existing cavitary and with/without intracavitary fungal balls; and (3) 'sub-acute invasive pulmonary aspergillosis' (rapidly progressive CNPA of < 3 months in duration) [3].

The spectrum of chronic pulmonary aspergillar infections depends upon the following factors: a) immunity conditions of the host (e.g., assumption of immunosuppressive drugs, patients with HIV infection, nephropathy or diabetes mellitus, oncologic patients); b) the anatomical integrity (previous lesions), functional alterations (bronchial obstruction) and mucociliary clearance of the respiratory system; and c) environmental *Aspergillus* load [1–7]. More specifically, patients with a previous history of tuberculosis, sarcoidosis, cystic fibrosis or others lung disease are most susceptible to aspergillosis. The diagnosis of CPA is difficult to make and, often, is delayed by an average of months or years, contributing to increasing its morbidity and mortality. Different diagnostic strategies are currently being used, including radiology (Chest X-ray and Chest CT), cultures (sputum culture, bronchoscopy or bronchoscopy with lavage, so called BAL), several serologic tests (*Aspergillus*-specific IgE and IgG antibodies using immunofluorescence or IFA and radial immunodiffusion methods or ELISA), and scintigraphic technique. According to Byung et al, diagnostic criteria for chronic pulmonary aspergillosis are clinical, radiological and laboratory [1, 2]. The diagnosis can be confirmed by demonstrating the invasion of the pulmonary tissue by septate hyphae typical of *Aspergillus* spp., and positive cultures of pulmonary tissue samples. This material is generally obtained through bronchoaspirate, transbronchial biopsy or transthoracic puncture, even if these procedures have been reported to have a low yield. In addition, although in advanced diseases the diagnosis can be made without difficulty by using modern technology, such as CT and MRI, in case of early disease it can be difficult to detect fungal infection. In addition, traditional scintigraphic techniques, particularly radiolabeled WBC imaging, suffer from substantial shortcomings, because they are time-consuming, labour intensive, costly, and the results may not be available before 24 hours, delaying the treatment [8]. However, the introduction of whole-body imaging techniques with FDG PET/CT has changed this situation. Scintigraphic techniques have been proposed including ^{67}Ga-citrate and F-18 fluorodeoxyglucose positron emission scanning (^{18}F-FDG PET/CT). FDG is a nonspecific tracer that has been found to accumulate at sites of infection, due to upregulation of cellular glucose metabolism. Therefore, PET/CT is considered as a powerful tool to diagnose, stage, and monitor patients with a variety of diseases; particularly, it is useful for the monitoring of disease activity and response to therapy, and can play a major role in the treatment of infections, including fungal infections. A research by Hot et al. showed that ^{18}FDG PET could support clinicians for the initial diagnosis and staging of invasive fungal infections [9]. Moreover, ^{18}F-FDG PET/CT could be useful during the follow up for differential diagnosis between active disease and evidence of organic damages as a result of the disease process [1, 10]. Therefore, the aim of our study was to evaluate the effectiveness of the ^{18}F-FDG PET/CT in estimating the metabolic activity of the fungal infection in CPA and its role

for the diagnosis and follow-up of the disease, monitoring the response to the treatment. More specifically, we evaluated the sensitivity of ^{18}F-FDG PET/CT in comparison with serological tests and the degree of agreement between these two diagnostic methods in diagnosis and follow-up of patients affected by CPA.

METHODS

From among 45 patients who presented with suspected CPA during the study period (2010 - 2017) at Centre for Aspergillosis, Pneumology Unit, Niguarda Ca' Granda Hospital, Milan, Italy, we selected 37 cases under treatment for aspergillosis infection. All patients gave their informed consent to participate in our study, which was approved by the Institutional Review Board at our hospital in accordance with Helsinki Declaration. In order to make diagnosis of proven or probable CPA, we used a combination of clinical, radiological and laboratory criteria. Clinical criteria included chronic pulmonary or systemic symptoms > 3 months, including at least one of weight loss, productive cough, or hemoptysis, and no overt immunocompromising conditions (e.g., hematological malignancy, neutropenia, organ transplantation). Laboratory tests included elevated levels of inflammatory markers (C-reactive protein or erythrocyte sedimentation rate) and either a positive serum *Aspergillus* precipitin test or isolation of *Aspergillus* spp. from the pulmonary or pleural cavity. Radiological criteria were presence of areas of parenchymal densification due to pulmonary fibrosis, cavitary pulmonary lesion with evidence of paracavitary infiltrates or new cavity formation or expansion of cavity size over time, with no dissemination [1, 2]. Conventional diagnostic examinations were performed before the execution of FDG-PET. Additional diagnostic test, such lung CT-MRI, bronchoalveolar lavage, endoscopy and/or tissue biopsy, were performed as clinically indicated. Minor criteria for diagnosis included culture findings for *Aspergillus* in sputum (variable sensitivity) and lung biopsies (commonly requested in aggressive disease).

Exclusion criteria included: a) any other infection; b) considerable comorbid medical - surgical or psychiatric conditions that may have interfered with our study; and c) inability to tolerate staying in a PET scanner for the duration of the examination [8]. Our patients were underwent PET/CT using ^{18}F-FDG following standard protocol, already adopted in past research [10]. PET/CT images were analyzed by qualitative method using the background activity as index of normal uptake. At the time of the first diagnosis, we studied agreement and compared sensitivity of PET and serologic tests (i.e., identification of *Aspergillus*-specific IgE and IgG antibodies using IFA or ELISA).

In a second step of the study, patients were treated with terbinafine (500 mg b.i.d.), which may be an effective and valid alternative to itraconazole for the treatment of chronic infectious forms of pulmonary aspergillosis, as shown in past studies [1, 10]. After administering antifungal therapy to our patients, at 6-12 months follow-up we repeated PET/CT using ^{18}F-FDG in patients with radiological picture of possible permanence of disease to detect the presence of active disease and make a comparison between serological tests and ^{18}F-FDG PET/CT for sensitivity and agreement. Indeed, differently from serological test, some researchers showed that ^{18}F-FDG PET/CT might be useful during the treatment and the follow-up period, in order to distinguish between pulmonary images associated with active disease and organic damages with no active disease [1, 5]. In our study, PET/CT and serological tests were classified in two types of diagnostic outcomes: a) positive; and b) negative categories. Cases of low-positive or borderline anti-*Aspergillus* IgG antibodies were considered as 'positive'.

Sensitivity was calculated as the proportion of positive results obtained with the index test among cases and confidence intervals for sensitivity were 'exact' Clopper-Pearson confidence intervals [11]. The agreement between diagnostic techniques was assessed using the Kappa coefficient. All of the kappa

coefficients were evaluated using the guideline outlined by Landis and Koch [12], where the strength of the kappa coefficients = 0.01 - 0.20 slight; 0.21 - 0.40 fair; 0.41 - 0.60 moderate; 0.61 - 0.80 substantial; 0.81 - 1.00 almost perfect, according to Landis and Koch [12]. The level of significance was set at 5% ($P < 0.05$). The analyses were performed using the statistical software SPSS, version 20.

RESULTS

Thirty-seven adult patients (21 males and 16 females) affected by CPA were recruited during the study period. The median age was 45 years (range: 35-73 years). Lung biopsies were performed on 3 of 37 (8%) patients and culture test for *Aspergillus* in bronchoalveolar lavage executed on 12 patients (32%). No adverse effect was observed after injection of the isotrope in the 37 patients who were evaluated by ^{18}F-FDG PET. At the time of first diagnosis, PET/CT findings were found positive in 31 out of 37 patients affected by CPA (84%), whereas serological test showed a higher sensitivity (i.e., in 35 out of 37 patients, 94% of the sample), with an 'almost perfect' agreement between (negative or positive) PET and serologic tests (88%, Kappa = 0.846, $P < 0.05$). However, for this calculation we considered as 'positive' 2 serological tests showing a low level of positivity. In one of the two cases of disagreement between PET (positive) and antibodies (negative), the sputum culture was found positive for *Aspergillus Fumigatus*. In 13 out of 31 patients with positive PET scan, an increased metabolic activity of the disease was also found at mediastinal lymphonodus. ^{18}F-FDG PET/CT scan was repeated only in 16 out of 37 cases during the follow-up at 12 months after the start of therapy. At 12 months follow-up, PET/CT findings resulted positive in 15 out of 16 patients (93%) affected by CPA, whereas serologic tests were positive in only 12 out of 16 patients (75%), with a 'good' agreement between them (81%, Kappa = 0.684, $P < 0.05$). Only one single negative PET exam finding was confirmed by negative serological test (see Figures 1A and 1B). Conversely, in 3 out of 4 cases in which serological test (*Aspergillus*-specific IgG antibodies) were negative, PET exams revealed evidence of active disease. Moreover, in 4 out of 5 patients with low-level of antibodies, there was a low-level of PET/CT positivity, too. Table 1 shows that, at the time of first diagnosis the degree of agreement between serological tests and 18F-FDG PET was higher (88%) than at 12-months follow-up (81%).

Table 2 summarizes the comparison of sensitivity between serology and 18F-FDG PET in our sample of patients affected by CPA, at first diagnosis and during their follow-up. Our data showed that at the time of first diagnosis serological test had a better sensitivity (94.59%, CI 95% 81.81% to 99.34%) than 18F-FDG PET (83.78%, CI 95% 67.99% to 93.81%).

On the contrary, at 12-months follow-up 18F-FDG PET reported higher sensitivity (93.75, CI 95% 69.77% to 99.84%) than serological test group (75%, CI 95% 47.62% to 92.73%).

DISCUSSION AND CONCLUSION

Our study assessed sensitivity and the degree of agreement between ^{18}F-FDG PET/CT and serological tests for diagnosis and follow-up of patients affected by CPA. Findings of our research showed an excellent agreement between ^{18}F-FDG PET and serological tests both at first diagnosis and, after the start of therapy, at 12 months follow-up in patients affected by CPA with active disease. This agreement was higher at first diagnosis. The lower level of both agreement and serological test sensitivity during follow-up confirmed the major role that PET/CT might play in monitoring of therapy. Sensitivity can be defined as the probability of getting a positive result in subjects with the disease and relates to the potential of a test to recognize subjects with the disease [13]. Comparing the sensitivity of these two diagnostic methods, serological tests showed a higher sensitivity than PET/CT at first diagnosis and vice versa at 12-months follow-up. In a prospective study Hot et al. [9] showed that the power of

Table 1. Agreement between serological test and 18F-FDG PET in patients with CPA at first diagnosis and during follow-up.

	At first diagnosis (*n* = 37)	**At 12-months follow-up (*n* = 16)**
Type of agreement	Almost perfect 88%, Kappa = 0.846*	Good 81%, Kappa = 0.684*

Statistical significance at P < 0.05 *

Table 2. Comparison of sensitivity between serological test and 18F-FDG PET in patients with CPA, at first diagnosis and during follow-up.

	At first diagnosis (*n* = 37)			
Category	**^{18}F-FDG PET**	**Aspergillus Antibody (IgG)**	**^{18}F-FDG PET Sensitivity (% 95% CI)**	**Aspergillus Antibody (IgG) Sensitivity (% 95% CI)**
Positive	31	35	83.78% (67.99%-93.81%)	94.59% (81.81%-99.34%)
Negative	6	2		
	At follow-up (*n* = 16)			
Category	**^{18}F-FDG PET**	**Aspergillus Antibody (IgG)**	**^{18}F-FDG PET Sensitivity (% 95% CI)**	**Aspergillus Antibody (IgG) Sensitivity (% 95% CI)**
Positive	15	12	93.75% (69.77%-99.84%)	75% (47.62%-92.73%)
Negative	1	4		

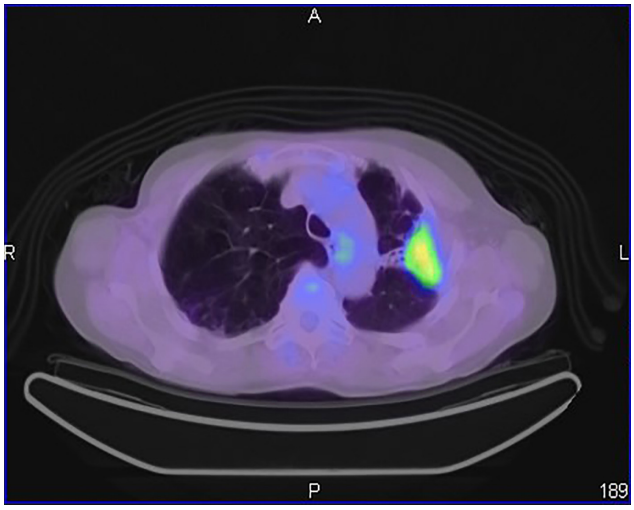

Figure 1A.

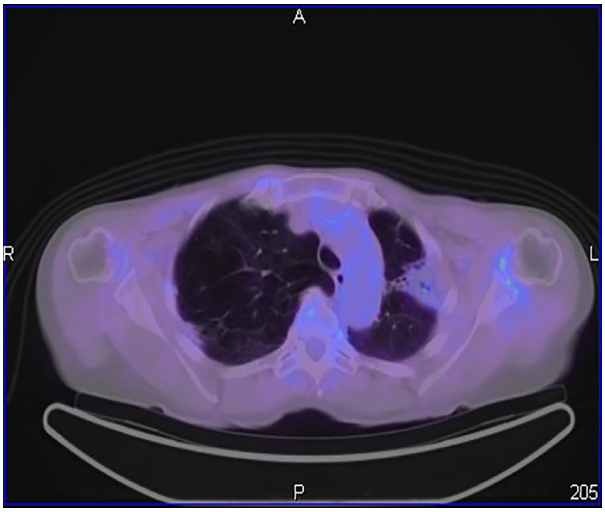

Figure 1B.

In Figure 1A ^{18}F-FDG PET/CT positive for pulmonary aspergillosis (before treatment). In Figure 1B ^{18}F-FDG PET/CT negative for pulmonary aspergillosis (after treatment) in patient affected by CPA with active disease.

^{18}F-FDG PET/CT to detect invasive fungal infections, had at least the same sensitivity as conventional imaging. In addition, these authors showed that PET/CT might be able to detect infectious foci that had not been identified with conventional techniques, in agreement with past studies carried out by Ho et al. [14] on four cases of lung and hepatosplenic candidiasis, and by other researchers about one invasive mould infections involving the

lung and brain and one case of lung cryptococcosis associated with ^{18}F-FDG intake [15]. In our study only in one case of active disease FDG PET/CT was negative, as well as serological tests.

In literature, it is well-recognized the important role of FDG PET/CT in pulmonary aspergillosis regarding the power of differentiation of invasive and non-invasive pulmonary aspergillosis [16, 17].

In our research, findings suggest that ^{18}F-FDG PET/CT might be able to detect active functional/metabolic changes reflecting inflammatory cell activity before the onset of abnormalities as assessed with conventional serological tests. This research confirms past research where ^{18}F-FDG PET/CT has been found to be a valuable tool for therapy monitoring in patients with aspergillosis [18]. In case of anti-Aspergillus antibodies positivity, FDG PET/CT could be useful to confirm the diagnosis of aspergillosis, whereas invasive methods such as BAL and pulmonary transcutaneous needle aspiration would be more costly and troublesome.

This study has some limitations. Firstly, the sample size is limited, and we were not able to study differences in specificity, accuracy, positive and negative predictive values between these two diagnostic procedures. Indeed, we were able to perform FDG PET/CT only when diagnosis of active disease in our sample of participants was considered as highly probable. In spite of these limitations, the results showed that the sample size was suitable for the assessment of sensitivity and agreement concerning the two diagnostic methods tested. ^{18}F-FDG PET/CT could be useful in detecting status of disease activity in patients treated with antifungal infections, showing whether anatomic pulmonary abnormalities are due to fibrosis as a result of chronic inflammatory process, or due to a nonresponse to antifungal treatment. Further, in our research we observed hypercaptation of the radiopharmaceutical agent used in the aspergilloma. This could suggest new solutions when surgical treatment is contraindicated. This finding is in agreement with past studies showing that FDG-PET sometimes shows accumulation in inflammatory and granulomatous conditions, such as aspergilloma [19]. However, in some cases pulmonary aspergillosis can mimic lung malignancy on FDG PET/CT, causing false-positive results and requiring histopathologic analysis to solve this important diagnostic dilemma [18–23]. Therefore, even if FDG PET/CT can raise the suspicion of fungal infection, culture or biopsy could be required for a specific diagnosis [9]. Finally, other PET tracers have been introduced for imaging of aspergillosis using ^{68}Ga-labeled compounds such as siderophores, but they require further research [24]. In conclusion, our findings indicate that ^{18}F-FDG PET/CT scan is a reliable support tool for clinical and serological data in the diagnosis and follow-up of aspergillosis infection, providing additional information on metabolic activity, accurate anatomic localization and extent of disease. ^{18}F-FDG PET/CT could be useful up for differential diagnosis between active disease and evidence of organic damages as a result of the disease process, giving precious information for the treatment duration, too. In case of doubt, when patient tests slightly positive for antibodies, ^{18}F-FDG PET/CT could confirm the presence of active disease and, at the same time, detect pulmonary areas that are affected by CPA, in order to facilitate fibrobronchoscopy and transcutaneous needle aspiration of the lung. Conversely, when antibodies are negative, negative ^{18}F-FDG PET/CT could be useful to confirm the patient's total recovery. Therefore, PET/CT may be considered as a powerful tool to diagnose, stage, and monitor patients with a variety of diseases; particularly, it is useful for the monitoring of disease activity and response to therapy, and can play a major role in the treatment of infections, including fungal infections like CPA. Therefore, our study is in agreement with past studies showing that ^{18}F-FDG PET/CT can be useful during the follow up for differential diagnosis between active disease and evidence of organic damages as a result of the disease process [1, 10], supporting clinicians for the

initial diagnosis and staging of invasive fungal infections [9]. This evidence confirms the major role of FDG PET/CT in literature to serve as a valuable tool in monitoring the treatment response to antifungal therapy [20].

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