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

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Keywords: ^{18}F-FDG-PET - CT - Fever of unknown origin

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Received:
24 September 2011
Accepted:
10 October 2011

Abstract

Determining the cause of fever of unknown origin (FUO) often proves challenging to attending physicians and the role of conventional imaging in this setting has been uncertain. In this retrospective study, we examined the role of fluorine-18 fluorodesoxyglucose-positron emission tomography (^{18}F-FDG-PET) compared to computed tomography (CT) in diagnosing the potential etiology of FUO. To accomplish this task, *we identified patients with FUO* who underwent ^{18}F-FDG-PET for detecting the source of fever. Twenty-four patients (16 males and 8 females, age range = 17-80, mean age = 49.5) were examined with ^{18}F-FDG-PET of which 18 were also assessed with a diagnostic CT (within 3 weeks, mean interval = 7.5 days). The PET and CT findings were reviewed and the presence of focal ^{18}F-FDG uptake or gross CT lesions was considered a potential site causing FUO. *Of patients who* underwent PET alone, 5/6 were reported as positive. Of the18 who had both PET and diagnostic CT, PET was positive in 18 and CT was positive in only 7 cases. Of positive findings on PET, etiologies included infection (11), non-infectious inflammation (8), lymphoma (3), and other cancers (1). Of positive findings on CT, etiologies included infection (3), lymphoma (1), non-infectious inflammation (2) and other cancers (1). Importantly, we found no cases with positive CT and negative PET findings. *In conclusion*, accordingly to our findings, ^{18}F-FDG-PET appears to be of great value in assessing patients with FUO, especially when caused by infection or inflammation. Fluorine-18 FDG-PET is more sensitive than diagnostic CT in detecting and localizing diseased sites, and is the optimal imaging modality to evaluate patients with FUO.

Hell J Nucl Med 2011; 14(3): 255-259 *Published on line: 10 November 2011*

Introduction

Determining the cause of fever of unknown origin (FUO) is perhaps the most challenging task in medicine. The practical and economic implications of the diagnostic workup of FUO are severely underappreciated. FUO is defined as an elevated temperature >38.3° C for more than 3 weeks duration and a failure to reach a clinical diagnosis despite one week of inpatient investigation. This definition was later revised by eliminating the requirement for in-hospital evaluation and excluding immunocompromised patients. Recently, the quantitative criterion (diagnosis uncertain after 1 week of investigation) has been changed to a qualitative criterion that requires a certain set of investigations to be performed [1-3]. The diagnostic approach in FUO includes a thorough history and physical examination, laboratory tests, as well as both conventional and novel imaging studies. Early identification and localization of the source of the fever can be critical for the management of these patients. Several studies have reported that the final diagnosis of FUO is established in only 33%-75% of cases [4-8]. Despite many modern investigative techniques, diagnosing the underlying cause of FUO remains elusive.

Three major categories that account for the majority of FUO cases are infections, malignancies and non-infectious inflammatory diseases. In general, infectious diseases explain about one-third of cases of FUO, followed by noninfectious inflammatory diseases (NIID) and then malignancy [9]. The category of NIID includes systemic rheumatoid diseases, vasculitis syndromes, granulomatous disorders, and auto inflammatory syndromes. There are, of course, the varying percentages of patients who present with FUO and fail to reach a final diagnosis as well.

The clinical algorithm employed to diagnose the etiology of FUO beings with a complete history, physical, and obligatory investigation that include: complete blood count, erythrocyte sedimentation rate, serum C-reactive protein, electrolytes, creatinine, total protein, protein electrophoresis, alkaline phosphatase, ALAT, LDH, creatine kinase, an-

tinuclear antibodies, rheumatoid factor, urinalysis, blood cultures (n=3), urine culture, chest X-ray, abdominal ultrasonography and tuberculin skin test [10-11]. When no source or clues to a source are identified from the aforementioned techniques, advanced imaging is required. While imaging provides a high-yield method to investigate possible causes of FUO, confirmatory tests are often used to establish a final diagnosis. These confirmatory techniques may include biopsy, immunological investigation, surgery, microbiological cultures, polymerase chain reaction or autopsy.

Imaging modalities used for the investigation of FUO include both anatomic and functional techniques. Abdominal ultrasound**,** including the pelvis**,** and a simple chest X-ray are usually the methods of first choice. If these techniques fail to elucidate an etiology, a variety of more advanced imaging modalities can be made available to the clinician for further investigation. Computed tomography (CT) and magnetic resonance imaging (MRI) can be employed to investigate structural changes of the body. Scintigraphic techniques, like gallium-67 scanning, indium-111 labeled leukocyte imaging and fluorine 18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) can be employed to look for molecular and metabolic alterations that underlie certain changes in tissue architecture.

Of the structural imaging techniques used in the workup of FUO, CT is often the modality of choice for its wide availability and high anatomic resolution. In FUO in particular, CT appears to be useful in identifying abnormalities of the hepatobiliary system, abdominal or pelvic abscesses and certain malignancies [12]. However, CT may produce false-negative results in the setting of abnormal anatomy, small abscess size, failure of appropriate contrast use, or early disease process. In a study by Lopez et al (2005), CT contributed data suggestive of the diagnosis in 41.7% of subjects whereas abdominal ultrasonography only gave useful orienting information in 8% of subjects [13]. Another study of the diagnostic effectiveness of CT for diagnosing the cause of FUO reported a sensitivity of only 29% [14]. These data suggest that the current standard for advanced imaging of FUO is unsatisfactory.

Functional imaging has the advantage of detecting early changes at the molecular level before any gross anatomical manifestations. By quantifying metabolic changes at the cellular level, functional imaging modalities have the ability to identify a disease process in its earliest stages. Traditionally, gallium-67 citrate (^{67}GaC) scanning was the most commonly used scintigraphic imaging technique for the evaluation of FUO because it can visualize malignancies, as well as inflammatory and granulomatous disorders [15]. This technique will be replaced by ^{18}F-FDG-PET and other nuclear medicine techniques for several reasons, because it has a high sensitivity for the detection of infection, inflammation and malignancy [16-21]. This technique is advantageous over ^{67}GaC because it can image the whole body in a short time, has high spatial resolution and delivers relatively low radiation doses to the patient. Others found the results of these two techniques to be comparable [22], but ^{18}F-FDG-PET is preferable due to the abovementioned practical advantages. Others also compared these two modalities for evaluating FUO and found ^{18}F-FDG-PET to be superior [23]. These authors reported a sensitivity of 81% and a specificity of 86% for ^{18}F-FDG-PET and a sensitivity and specificity of 67% and 78%, respectively, for ^{67}GaC scanning. These data strengthen the argument for the role of ^{18}F-FDG-PET over other imaging modalities in the diagnostic workup of fever of unknown origin.

Furthermore, the advent of fused PET/CT imaging may greatly improve diagnostic results of imaging in the setting of FUO due to its ability to unite the advantages of molecular and morphological investigations. In a retrospective study of 48 patients who underwent ^{18}F-FDG-PET/CT due to fever of unknown origin, the PET/CT interpretation was suggestive of the final diagnosis in 46 cases and others reported a 97% sensitivity and 75% specificity [24]. Increasingly, numerous clinical centers around the world are now choosing to employ ^{18}F-FDG-PET/CT as part of the diagnostic workup for FUO due to its improved sensitivity.

However, since there is no gold-standard algorithm, or imaging modality to investigate potential causes of FUO, we explored data from our own center to appropriately determine the role of ^{18}F-FDG-PET compared to CT in diagnosing FUO. We not only characterize our own institution's capacity to diagnose etiologies of FUO, but also, we provide further evidence for the role of functional imaging, specifically ^{18}F-FDG-PET, in difficult to diagnose clinical scenarios such as FUO.

Methods

Patient population

We conducted a retrospective search of patients who underwent ^{18}F-FDG-PET and/or diagnostic CT for the diagnosis of fever of unknown origin at the Hospital of the University of Pennsylvania from 2005 until present. Our search was conducted using key words in the 'report search' function within the University's IDXrad system to identify the reason for imaging. This search ultimately produced a group of imaging reports that were ordered for the diagnostic workup of FUO. This study included 24 patients (16 males and 8 females, age range = 17-80, mean age=49.5). Of those who were examined with ^{18}F-FDG-PET, 18 were also assessed with a diagnostic CT (within 3 weeks of each other, mean interval, 7.5 days).

Imaging acquisition

Whole-body PET started at a mean time point of 60min after the injection of 2.52MBq/kg body weight. At the time of ^{18}F-FDG injection, all patients had fasted for at least 4h and had blood sugar levels of <150mg/dL. Scans included the neck, thorax, abdomen, pelvis and upper thighs. Images consisted of four or five emission frames that were 25.6cm in length, with an overlap of 12.8cm covering an axial length of 64-76.8cm. Image reconstruction was performed with an iterative ordered-subset expectation maximization algorithm with four iterations and eight subsets. Attenuation-corrected images were obtained by applying transmission maps with a cesium-137 source interleaved with emissions scans.

CT Imaging by CT of abdomen, chest and pelvis was performed on a single (GE Prospeed 9 patients; General Electric, Waukesha, WI) or multidetector row CT scanner (GE Lightspeed QXi, 4 slice detector 7 patients; General Electric, Waukesha, WI and Siemens Sensation 16 slice detector 2 patients; Siemens, Malvern, PA) using a 5mm or

7mm slice thickness, kVp of 120, and a mean mA of 223 (range 120-412).

Image interpretation and analysis

The PET and CT written reports were retrieved from IDXrad and reviewed by three experienced nuclear medicine physicians. In order to determine the utility of each imaging modality in the diagnostic work-up of each patient, potential diagnostic findings were identified and recorded. The presence of focal FDG uptake or gross CT lesions, defined by the interpreting physician was considered a potential site causing FUO. These potential findings were compiled in a spreadsheet and categorized into etiologies of infection, non-infectious inflammation, lymphoma, other neoplasm, or no finding based upon the final diagnoses evident in the patient chart. Final diagnosis was determined by histopathology, culture, pertinent lab values, or serial imaging depending on the context, but was ultimately referenced from the attending physician's clinical notes. For each imaging modality, we determined etiological distributions using standard statistical techniques. We also determined overall specificity for each imaging modality, considering the type of imaging used and the interpreting physician's radiographic findings.

Results

Of patients who underwent PET alone, 5/6 was reported as positive (83.3%). Of 18 who had both PET and diagnostic CT, PET was positive in 18 (100%) and CT was positive in only 7 (38.9%) cases. Of positive findings on PET, etiologies included infection (47.8%), non-infectious inflammation (34.8%), lymphoma (13%), and other cancers (4.4%). Of positive findings on CT, etiologies included infection (42.8%), lymphoma (28.6%), non-infectious inflammation (14.3%), and other cancers (14.3%). There were no cases with positive CT and negative PET findings (See Table 1 and Figure 1).

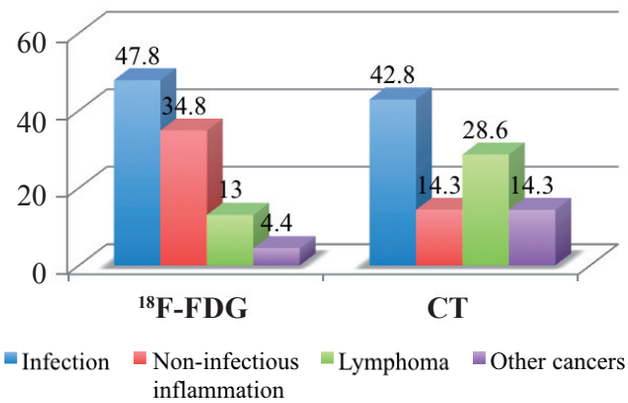

Figure 1. Categorical breakdown of etiologies of FUO

Discussion

Revealing the cause of FUO poses a significant diagnostic challenge. Fever of unknown origin is often frustrating for patients and physicians alike because the diagnostic workup involves numerous noninvasive and invasive procedures that fail to explain the fever. In FUO, there is no obvious diagnostic gold standard against which other diagnostic tests may be compared. Although diagnostic clues can be quite variable, it is clear that imaging plays a crucial role in aiding the diagnostician.

Data from this study and others support the notion that ^{18}F-FDG-PET is of great value in assessing patients with FUO, especially when caused by infection or inflammation. Computed tomography appears to be of low clinical yield because it selectively detects only structural changes which can either happen too late in the disease process, or not at all. Additionally, CT suffers from the inability to provide quantitative information in order to differentiate between active and quiescent, or benign and malignant lesions. For the all the shortcomings of CT in the arena of working up FUO, ^{18}F-FDG-PET succeeds (See Figures 2-4). In this setting, PET boasts superior sensitivity, localization of active lesions in the body, and more robust quantitative data compared to structural techniques. When combined with a confirmatory biopsy, the routine use of ^{18}F-FDG-PET could help improve diagnosing etiologies of FUO [25]. This test is also superior in its ability to help distinguish between categories of lesions e.g. inflammatory versus neoplastic. The combination of anatomic imaging fused with molecular imaging is currently paving the way as the modality of choice for a number of indications. We understand that a limitation within our study is the comparison of dedicated ^{18}F-FDG-PET versus ^{18}F-FDG-PET/CT, but we chose to include patients from 2005 to include as many subjects as possible. Hybrid technology of PET/CT will ultimately aug-

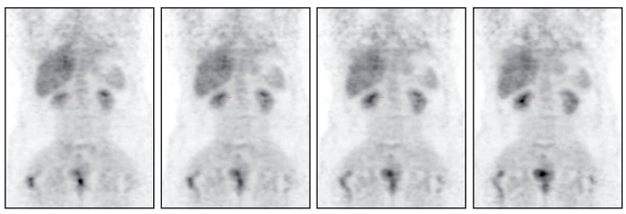

Figure 2. Images of ^{18}F-FDG-PET in a patient with FUO that pinpointed the cause of fever to be an infected hip, confirmed by culture. This series demonstrates the advantage of functional imaging.

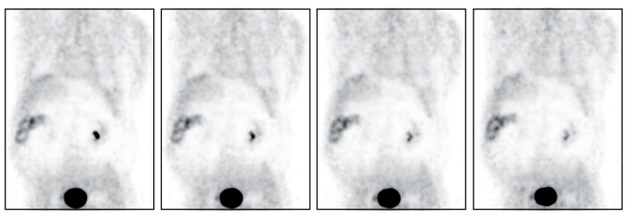

Figure 3. Images of ^{18}F-FDG-PET in another patient demonstrate clear evidence for inflammatory bowel disease in the hepatic flexure region, which was the cause of this patient's fever. Final diagnosis was reached by intestinal biopsy.

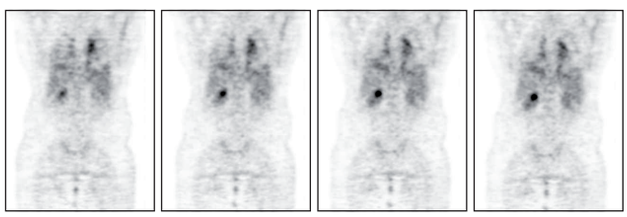

Figure 4. Images of ^{18}F-FDG-PET in a patient with FUO. These images demonstrate the underlying pathology, which turned out to be lung carcinoma, confirmed by surgical pathology.

Table 1. *Patients included in our retrospective study. Final diagnosis determined by patients' attending physician clinical notes - based on combination of imaging, histopathology and lab values*

Patients-Age-Gender	PET	CT	PET findings	CT findings	Final diagnosis	Category of diagnosis
86y M	Y	Y	+	+	Parotitis	Inflammation
40y F	»	»	+	-	Stent graft infection	Infection
22y M	»	»	+	-	Pelvic abscess	»
35y »	»	»	+	-	Pneumonia	»
47y »	»	»	+	-	Aortopulmonary window infection	»
20y F	»	N	+		J-tube infection	»
17y M	»	»	+		Pneumonitis	Inflammation
80y »	»	Y	+	-	Megacolon	Infection
60y »	»	N	+	-	IBD	Inflammation
17y F	»	»	+	-	Oophoritis	»
68y F	»	Y	+	+	Pneumonia	Infection
38y M	»	»	+	-	Lymphoma	Lymphoma
50y F	»	»	+	-	Hip abscess	Infection
22y »	»	»	+	+	Caroli's disease	Inflammation
78y M	»	»	+	-	Biliary inflammation	»
74y »	»	»	+	+	Lymphoma	Lymphoma
79y »	»	»	+	+	Pneumonia	Infection
46y »	»	»	+	+	Lymphoma	Lymphoma
59y F	»	»	+	-	Thyroiditis	Infection
59y M	»	N	+		Lung cancer	Neoplasm
69y »	»	Y	+	-	Pneumonitis	Inflammation
65y »	»	»	+	-	Hip absc ess	Infection
23y »	»	»	+	-	IBD	Inflammation
53y F	»	N	-		Undiagnosed	

Y=yes. N=no. (+) = positive finding. (-) = negative finding. M=male. F=female.

ment the accuracy of the FUO workup. As noted from our results, ^{18}F-FDG-PET is more sensitive than CT in detecting and localizing diseased sites [26-28], and it is likely that PET-CT will soon be regarded as the optimal imaging modality to evaluate patients with FUO.

The authors declare that they have no conflicts of interest.

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