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JMED Research
http://www.ibimapublishing.com/journals/JMED/jmed.html
Vol. 2014 (2014), Article ID 389734, 13 pages
DOI: 10.5171/2014.389734

Research Article

Role of ^{18}F-FDG PET-CT in Vasculitis: A Prospective Study

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Received date: 10 January 2014; Accepted date: 3 July 2014; Published date: 31 December 2014

Academic Editor: Ion Codreanu

Abstract

Objective: Evaluate the diagnostic accuracy of PET in patients with fever of unknown origin (FUO) and in patients with suspected and/or proved large vessel vasculitis (LVV). **Patients and methods:** 72 patients (49 females, 23 males; mean age 63 y, range 23-82) were prospectively examined with PET between February 2010 and April 2013; 42 with suspected LVV, 15 with LVV during steroid therapy, and 15 with fever of unknown origin (FUO). Follow-up scans were performed in 19 patients. A semi-quantitative analysis [Vessel SUVmax]/[liver SUVmax] was performed to rate the disease in a 4-step system. PET scans were compared with temporal artery biopsy and MRI and/or angio-CT of a specific region. **Results:** Pathological ^{18}F-FDG (FDG) uptake was observed in 30/72 (42%) patients, and negative in 42/72 (58%) patients. In 42 patients with suspected LVV 9 (21%) were positive, and 33 (79%) negative; 11 (73%) of the 15 steroid-treated patients with LVV were positive, and 4 (27%) negative; 10 (67%) of the 15 patients with FUO were positive and 5 (33%) negative. PET had an overall sensitivity of 87% [95% confidence interval (CI) 79-95%], a specificity of 95% (95% CI 90-100%), a positive predictive value of 93% (95% CI 87-99%) and a negative predictive value of 91% (95% CI 84-97%). The diagnostic accuracy of PET was 92% (95% CI 85-98%). **Conclusions:** ^{18}F-FDG PET/CT especially that based on semi quantitative analysis is a sensitive and specific imaging tool for the diagnosis of LVV but also for therapy monitoring and follow up.

Keywords: vasculitis, FDG-PET/CT, corticosteroid therapy

Cite this Article as: Kinga Diana Siczek, Paola Faggioli, Emanuela Venegoni, Luigia Florimonte, Marco Carletto, Fabio Cammelli, Cristina Songini, Alberto Vignati, Rossella Stoico, Antonino Mazzone and Lorenzo S. Maffioli (2014)," Role of 18F-FDG PET-CT in vasculitis: a prospective study ", JMED Research, Vol. 2014 (2014), Article ID 389734, DOI: 10.5171/2014.389734

Introduction

The diagnosis of large vessel vasculitis (LVV), as Giant cell arteritis (GCA) and Takayasu's arteritis (TA), in clinical practice is often a difficult task, and it usually requires time and financial resources in order to define the characteristics of disease in patients with nonspecific symptoms and elevated inflammatory markers. In particular, two subsets of patients are a diagnostic challenge: 1) patients with fevers of unknown origin (FUOs), who can be classified into 4 main clinical categories: infectious, malignant, rheumatic-inflammatory and miscellaneous disorders (Meller et al. 2007, and Roth et al. 2003); 2) patients with increased inflammatory markers and systemic signs/symptoms in the absence of infections or tumors, (Gaeta et al. 2006).

Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitis (2013), (Jennette et al. 2012), classified vasculitis by:

1) Vessel diameter
2) Presence of granulomatous lesions
3) Presence of antineutrophil cytoplasmic antibodies (ANCA).

Standard diagnostic procedures include laboratory tests, biopsy, angiography, ultrasound and magnetic resonance angiography (Fuchs 2012), although these conventional diagnostic methods are not adequate to make a definitive diagnosis in approximately 50% of patients in this small group.

In studies by Mukhtyar (2009) and Basu (2012), laboratory tests, including erythrocyte sedimentation rate (ESR), C-reactive protein (PCR) and ANCA antibodies, were found to be nonspecific for large vessel vasculitis diagnosis.

Conventional imaging techniques such as Computed Tomography – (CT), angio-Computed Tomography (angio-CT), Magnetic Resonance (MR) and/or angio - Magnetic Resonance (angio-MR), ultrasound, and biopsy can be invasive, operator dependent, and often biased during disease duration and therapy. In particular MR takes relatively long time, can study only one region at time and cannot be performed in patients with pace maker. Angio-CT cannot be performed in patients with kidney disease because of the contrast.

Positron emission tomography-computed tomography (PET/CT), instead, is a noninvasive, operator independent, metabolic imaging modality based on the regional distribution of the glucose analogue (fluorine-18 fluorodeoxyglucose – 18F-FDG) (Fuchs 2012) and can be performed in all kinds of patients. In retrospective studies by Cao (2012), Qiu (2012), Watts (2009), Tezuka (2012), Talarico (2012) and Pipitone (2008) the performance of FDG PET/CT to diagnose vasculitis, rheumatic diseases, inflammatory diseases, and peritoneal fibrosis was evaluated usually enrolling a low amount of patients.

Sheng (2011), Cao (2012) and Qiu (2012) suggested that for the correct diagnosis with PET the addition of conventional imaging techniques may generally offer improved diagnostic accuracy compared with current standards of practice.

The aim of this study was the diagnostic accuracy of PET in patients with fever of unknown origin (FUO) and in patients with suspected and/or proved large vessel vasculitis treated with and without immunosuppressive drugs, and the possibility of the use of PET in these diseases' monitoring and treatment.

Patients and Methods

Patients

72 patients (49 females, 23 males; mean age 63 y, range 23-82), who were referred to our interdisciplinary centre in the Department of Rheumatology, were prospectively examined with PET imaging between February 2010 and April 2013; 42 with suspected large vessel vasculitis (LVV) 15 with (LVV) during steroid therapy (over 5 mg of prednisone/day) and 15 with fever

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of unknown origin (FUO). Follow-up scans were performed in 19 patients. Diagnoses were based on the American College of Rheumatology (ACR) classification criteria, laboratory tests, conventional imaging (angio-MRI and/or angio-CT, and/or ultrasound), on temporal artery biopsy in some patients and the exclusion of other diagnoses (Tab 1).

According to validated diagnostic criteria for vasculitis and for FUO, these are the main criteria we used to have our patients undergo PET imaging (13, 4), (Tab. 2 and Tab. 3).

Table 1: Patient studied with PET/CT

P	Age	Sex	Pathology	Laboratory	Cortisonic therapy	PET/ CT	FU PET/CT	Bio psy	C.I.
1	63	F	Vasculitis in tp	ESR ↑CRP↑	Yes 25 mg	Pos	Neg	Yes	Yes
2	60	M	Aortitis in tp	-	Yes 25 mg	Pos	Neg	Yes	Yes
3	42	F	Suspected aortitis	ESR ↑CRP↑	No	Neg	-	No	Yes
4	63	F	Suspected arteritis in AR	ESR ↑CRP↑	No	Pos	-	No	Yes
5	27	F	Suspected aortitis	-	No	Neg	Pos/neg	No	Yes
6	73	M	Suspected arteritis in PMR	-	No/7.5 mg	Neg	Neg/neg	No	Yes
7	78	F	Suspected arteritis	ESR ↑CRP↑	No	Pos	-	No	Yes
8	59	M	FUO	ESR ↑CRP↑	No/yes/yes/ yes	Pos	Neg/neg /neg	No	Yes
9	66	F	Vasculitis in tp	ESR ↑CRP ok	Yes/yes	Pos	Pos	No	Yes
10	79	F	Vasculitis in tp	ESR ↑CRP↑	Yes 2,5 mg	Pos	-	Yes	Yes
11	44	M	Suspected vasculitis	-	No	Neg	-	No	-
12	56	F	Suspected vasculitis	-	No	Neg	-	No	Yes
13	77	F	FUO	-	No	Neg	-	No	Yes
14	80	F	Suspected vasculitis	ESR ↑CRP↑	No/yes 10mg	Pos	Neg	No	Yes
15	59	M	Suspected vasculitis	ESR ↑CRP↑	No	Neg	-	No	Yes
16	23	F	Suspected vasculitis	ESR ↑CRP↑	No	Neg	-	No	Yes
17	48	F	FUO	-	No	Neg	-	No	Yes
18	79	M	Horton a in tp	-	-	Neg	-	No	Yes
19	77	F	Suspected vasculitis	-	No	Neg	-	-	-
20	77	F	FUO in PMR	ESR ↑CRP↑	No	Neg	-	Yes	Yes
21	69	F	Suspected vasculitis	-	No	Neg	-	No	Yes
22	61	F	FUO	ESR ↑CRP↑	No/yes	Pos	Neg	No	Yes
23	65	F	Suspected arteritis	-	No	Neg	-	No	Yes

P	Age	Sex	Pathology	Laboratory	Cortisonic therapy	PET/CT	FU PET/CT	Biopsy	C.I.
24	77	M	Arteritis in tp	ESR ↑CRP↑	Yes 15 mg/No	Pos	Neg	No	Yes
25	62	F	FUO	ESR ↑CRP↑	No/yes/yes	Pos	Pos/pos	No	Yes
26	72	F	Suspected arteritis	-	No	Neg	-	No	Yes
27	73	M	Suspected vasculitis	ANA pos, ANCA, antiDNA,ENA neg	No	Neg	-	No	Yes
28	60	F	Horton a in tp	-	Yes/ yes 5 mg	Pos	Neg	No	Yes
29	50	F	Suspected vasculitis	ESR ↑CRP↑	No	Neg	-	No	Yes
30	68	M	Suspected vasculitis	ESR ↑CRP↑	No	Neg	-	Yes	Yes
31	64	F	FUO	ESR ↑CRP↑	No/yes 20 mg/yes 5 mg	Pos	Neg/neg	No	Yes
32	55	M	FUO	ESR ↑CRP↑	No/yes 7.5 mg	Pos	Neg	No	Yes
33	45	M	Suspected vasculitis	-	No	Neg	-	No	-
34	38	F	Suspected vasculitis	-	No	Neg	-	No	-
35	72	M	Vasculitis in tp	-	Yes 7,5 mg	Neg	-	No	Yes
36	58	F	Suspected vasculitis	ESR ↑CRP↑	No	Neg	-	No	Yes
37	63	F	FUO	ESR ↑CRP↑	No	Neg	-	No	Yes
38	57	F	Suspected vasculitis	ESR ↑CRP↑	No	Neg	-	No	Yes
39	82	F	FUO	ANCA pos	Yes 25 mg/yes 5 mg/yes 7.5 mg	Pos	Neg/neg	No	Yes
40	76	M	FUO	-	No/no	Pos	Neg	No	Yes
41	70	M	Suspected vasculitis in AP	ESR ↑CRP↑	Yes 5 mg	Neg	-	No	Yes
42	30	F	FUO	ESR ↑CRP↑	No	Neg	-	No	Yes
43	38	F	Suspected vasculitis	-	-	Neg	-	No	Yes
44	72	F	Suspected vasculitis in PMR	-	-	Neg	-	No	Yes
45	68	M	Vasculitis in tp	ANCA pos	Yes 5 mg	Neg	-	No	Yes
46	24	M	Suspected vasculitis	-	No	Neg	-	No	Yes
47	49	F	Suspected vasculitis	CRP ok ANA, ENA, ANCA neg,	Yes	Neg	-	No	Yes
48	73	F	Suspected vasculitis in AR	ANA, ENA, anti DNA neg;	No	Neg	-	No	Yes
49	81	M	Suspected aortitis	ESR ↑CRP↑	No	Pos	-	No	Yes
50	69	F	Suspected vasculitis	ESR ↑CRP↑	Yes 4 mg	Neg	-	No	Yes
51	72	F	Suspected vasculitis	ESR ↑CRP↑ ANCA pos	Yes 4 mg	Neg	-	No	Yes
52	72	F	Suspected vasculitis	ESR ↑CRP↑	No	Neg	-	No	Yes
53	75	M	Suspected vasculitis	ESR ↑CRP↑	Yes 5 mg	Pos	-	No	Yes
54	60	F	Suspected vasculitis	ESR ↑CRP↑	No	Neg	-	No	Yes
55	72	M	Suspected vasculitis	ANA pos	Yes 5 mg	Neg	-	No	Yes

P	Age	Sex	Pathology	Laboratory	Cortisonic therapy	PET/CT	FU PET/CT	Biopsy	C.I.
56	79	F	Suspected vasculitis	ENA pos; ANA, anti DNA neg	No	Pos	-	No	Yes
57	67	F	Suspected vasculitis	ESR ok ANA pos, ENA, antiDNA neg	No	Neg	-	No	Yes
58	70	M	Suspected vasculitis	ESR↑	No	Neg	-	-	Yes
59	64	F	Suspected vasculitis	ESR ↑CRP↑ ANA, ENA, anti DNA neg	No	Neg	-	No	Yes
60	57	F	Vasculitis in tp	ESR ↑CRP↑	Yes	Neg	-	No	Yes
61	74	F	FUO	ESR ↑	No	Pos	-	Nd	Yes
62	63	F	FUO	ESR↑, ANA pos	No/yes 25 mg/yes 25 mg	Pos	Pos/pos	No	Yes
63	62	F	Suspected vasculitis	-	No	Pos	-	-	Yes
64	65	F	Suspected vasculitis	-	No	Pos	-	-	Yes
65	70	F	Vasculitis in tp	-	Yes	Pos	-	-	Yes
66	58	F	Vasculitis in tp	-	Yes	Pos	-	-	Yes
67	63	M	Vasculitis in tp	-	Yes	Pos	-	-	Yes
68	63	M	Vasculitis in tp	-	Yes	Pos	-	-	Yes
69	77	F	Suspected vasculitis	ESR ↑CRP ok	Yes/no	Pos	Neg	No	-
70	68	M	Vasculitis in tp	ESR ↑CRP ok, ANA, ENA, ANCA, antiDNA neg	Yes 25 mg	Pos	-	No	Yes
71	70	F	FUO	ESR ↑CRP↑ ANA pos, ENA neg	Yes 25 mg/yes 7.5 mg	Pos	Pos	No	Yes
72	67	F	Suspected vasculitis	ESR ↑CRP↑ ANA, ENA, ANCA neg	No/yes/yes 5 mg	Neg	Neg/neg	No	Yes

P = patients; FU = follow up with PET/CT; C. I. = conventional imaging (angio-CT, angio-RM, ultrasound); F = female; M = male; tp = therapy (corticosteroid therapy); Pos = positive; Neg = negative; ESR = Erythrocyte sedimentation rate; CRP = C-Reactive protein; ANA = antinuclear antibodies; antiDNA = native DNA antibodies; ENA = Extractable nuclear antigens; ANCA = Antineutrophil cytoplasmic antibodies; FUO = Fever of unknown origin

Table 2: Vasculitis diagnostic main criteria

1) Systemic	weight loss, nausea, fatigue, fever, malaise, night sweats
2) Temporal arteritis	jaw claudication, temporal artery thickening or local headache, eyesight abnormalities, myalgia and polymyalgia-like rheumatic symptoms
3) Cardiovascular	arterial claudication, peripheral pulse weakness, echocardiographic ultrasound abnormalities
4) Pulmonary	non infectious pulmonary infiltrates and interstitial lung diseases
5) Neurological	dizziness, headache, ischemic attack, polyneuropathy
6) Laboratory tests	increased C-Reactive Protein (CRP), increased Erythrocyte Sedimentation Rate (ESR), increased creatinine, positivity to Antinuclear Antibodies (ANA), native-DNA Antibodies (anti-n-DNA Ab), Extractable Nuclear Antigens (ENA), Antineutrophil Cytoplasmic Antibodies (ANCA)

Table 3: FUO main diagnostic criteria (PET should be performed before bone marrow biopsy).

1)	Negative bacterial cultures
2)	Negative serologic tests
3)	Negative total body CT scans
4)	Negative echocardiography

The study's endpoint was the diagnostic accuracy of PET for large vessel vasculitis (LVV) patients treated with and without immunosuppressive drugs, and the possibility of the use of PET for disease monitoring and treatment.

All scans were acquired after a 6hour fast, using an integrated PET/CT camera (PHILIPS GEMINI TF), equipped with a full-ring dedicated PET scanner and a sixteen slice CT scanner. The serum glucose level was measured before ^{18}F-FDG administration in all patients and was below 120 mg/dl (Glucometer Breeze 2, Bayer Diagnostics). PET scans were performed 60 min after intravenous injection using a venous line of 3,7 MBq/Kg body weight of ^{18}F-FDG. Low dose CT (max 120 Kv, 100mAs) and PET scans were performed from the base of the skull to the mid thigh. We performed whole-body scans using 3D acquisition with 7-8 contiguous bed positions (2min/bed). Iterative ordered subset expectation maximization (OSEM) reconstruction algorithm was used to obtain 512x512 format trans-axial slices of 4-5 mm thickness; CT attenuation correction was performed. Philips Imaging software was used to view and analyze the reconstructed images in PET-CT fusion modality.

PET Imaging* and *Statistical analysis

All scans were assessed by a panel of board certified nuclear medicine specialists.
PET scans were analysed visually in a descriptive manner, as well as by a quantitative computed method.

First visual analysis was performed. Thereafter, image readings were divided into three groups: normal vessel uptake, abnormal uptake in vessels with atherosclerotic plaque, and abnormal uptake in vessel without atherosclerotic plaque (Fig 1a, 1b, 1c).

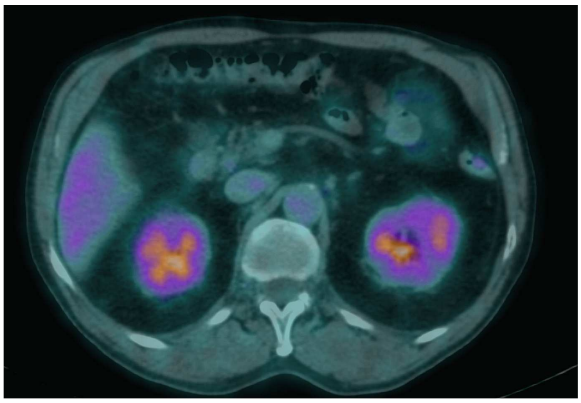


Figure 1A: Regular aorta uptake

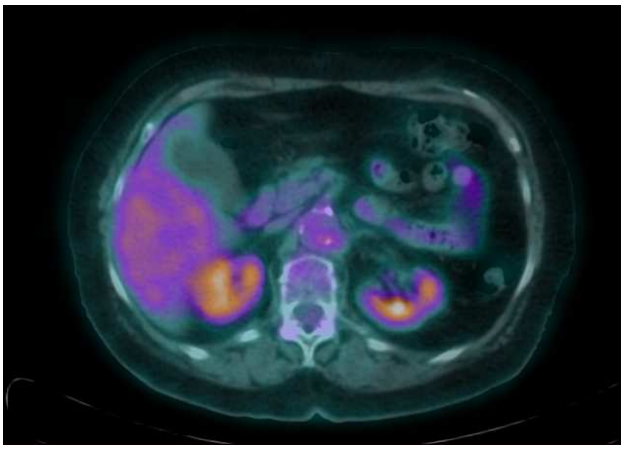


Figure 1B: Atherosclerotic plaque in aorta irregular uptake Vessel/liver ratio 1

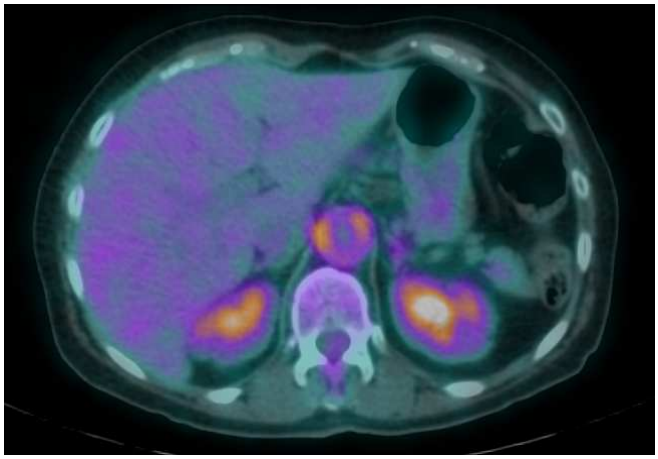


Figure 1C: Vasculitis vessel/liver ratio 1,8

Figure 1: FDG uptake in normal aorta wall (FIG 1A); FDG uptake in atherosclerotic wall of aorta (Fig 1 B): calcific plaque were considered as false positives; FDG uptake in vasculitis (Fig 1 C).

For quantitative evaluation, region of interest (ROI) was placed over nine defined vascular areas (ascending thoracic aorta, descending thoracic aorta, abdominal aorta, right and left subclavian arteries, right and left external carotid arteries, right and left common iliac arteries) and right hepatic lobe.

Using regions of interest SUVmax vessel to liver ratio was calculated and rated into 4 Grades. The means and standard deviations were calculated for orderly vessel/liver uptake ratio distributions, divided into two groups: negative (<1.0) and highly positive (≥ 1.0). For each group, the normal distribution was computed. Statistical analysis calculated different intervals (vessel/liver ratio < 0.9 was considered grade 0; vessel/liver ratio between 0.9 and 1 was considered grade I; vessel/liver ratio between 1 and1.1 was considered grade II; vessel/liver ratio ≥ 1.1 was considered grade III). Grade II and III were considered pathological.

Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of FDG PET/CT were calculated using clinical criteria and conventional imaging as the reference standard.

Results

The reference point for highly positive cases (≥ 1.1, blue area) was identified by the overlap of the two normal distributions. The mildly and moderately positive grades (mild: range 0.9- <1.0, orange area, and moderate: range 1.0- <1.1, green area) were defined by the presence of the positive distribution tail subtending the negative normal distribution (Fig2).

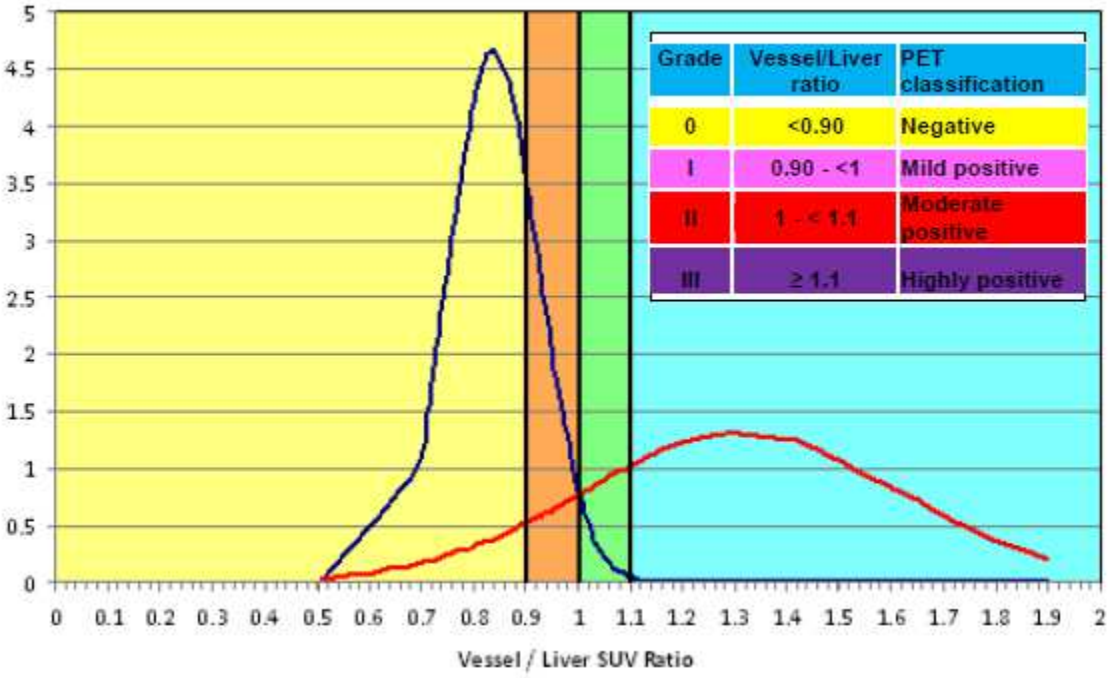


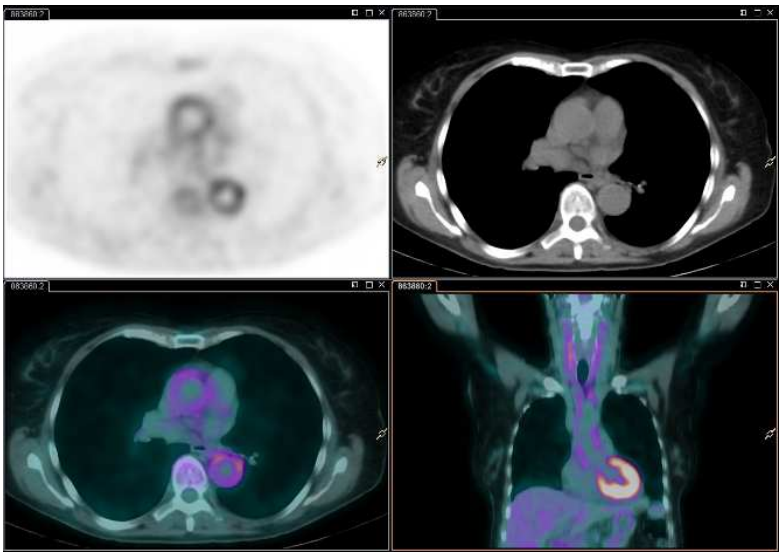
Figure 2: Normal distribution of SUVmax vessel/liver ratio; a semiquantitative analysis on (vessel SUV max)/(liver SUV max) was performed to rate the disease into a 4-step system

Using a semiquantitative analysis based on SUV max vessel to liver ratio, PET scans were considered positive for large vessel vasculitis in 30/72 (42%) patients, and negative in 42/72 (58%) patients. In 42 on PET scan, and 4 (27%) negative; in 15 patients with fever of unknown origin patients with suspected LVV: 9 (21%) were positive on PET scan, and 33 (79%) were negative; in 15 patients with LVV during steroid therapy: 11 (73%) were positive

(FUO): 10 (67%) were PET positive and 5 (33%) negative (Table 4, Fig 3).

Table 4: FDG PET/CT results

FDG PET	Suspected vasculitis	Vasculitis in steroid therapy	FUO
Positive (Grade II - III)	9	11	10
Negative (Grade 0 – I)	33	4	5
Total	42	15	15



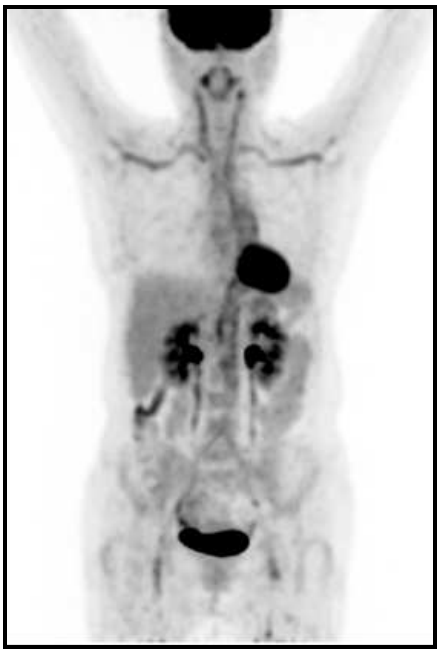


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Figure 3: FUO pre-therapy: vessel to liver ratio 1,6 (Fig 3A1-2); FUO post-therapy: vessel to liver ratio 1 (Fig 3B1-2).

Considering clinical criteria and conventional imaging, PET had an overall sensitivity of 87% [95% confidence interval (CI) 79-95%], a specificity of 95% (95% CI 90-100%), a positive predictive value of 93% (95% CI 87-99%) and a negative predictive value of 91% (95% CI 84-97%). The diagnostic accuracy of PET was 92% (95% CI 85-98%).

As reported by Fuchs et al.(2012), specificity and sensitivity of PET can be lower (64.5%) in patients on immunosuppressive or steroid therapy than in untreated patients. In our analysis we have considered all patients on steroid therapy as treated (over 5 mg of prednisone/day) because statistically significant differences were found.

We also utilized PET to detect therapy response in 19 patients affected by LVV. These patients were evaluated at baseline and at a different time point of follow up (when clinical relapse was evident or after steroid therapy reduction or withdrawal). Even if the number of patients was low for statistical analysis we could see a good correlation between positivity of PET and clinical symptoms.

Discussion

The diagnosis of large vessel vasculitis (LVV) is often difficult, and it usually requires time, money and discomfort for the patient. The diagnosis of small vessel vasculitis is still histological.

As reported by Hooisma (2012), the diagnostic standard method for LVV, especially in giant cell arteritis (GCA), is a temporal artery biopsy, but the test results can be false negative in 15-70%, which may delay the diagnosis; in Takayasu's arteritis (TA), which affects the aorta and its main branches, as well as the coronary and pulmonary arteries, routine histological examination is not suitable.

Several methods such as Color Doppler Sonography (CDS), Magnetic Resonance (MR) and Computed Tomography (CT) have been proposed to evaluate LVV. As reported by Pipitone et al. (2008) these tools (CDS, MRI, CT) revealed their usefulness in detecting early vasculitic lesions (mainly presented as an alteration of vessel lumen), while only angiography was able to detect delayed effects of LVV (e.g. aneurism or vascular stenosis).

Besson and coworkers (2011) reported in their meta-analysis that diagnostic performance of FDG-PET in giant cell arteritis provided sensitivity and specificity of 80% and 89%, respectively.

In their study, Ergul (2011) and Hooisma (2012) highlighted the utility of PET in early diagnosis of LVV and in discovery of occult inflammatory or neoplastic disorders.

In our study, the sensitivity and specificity of PET are high, with lower risk to patients with respect to other diagnostic methods (such as angiography or CT/MR angiography). As previously reported by Fuchs et al., ^{18}F-FDG PET/CT increases the overall diagnostic accuracy and has an impact on the medical management in a significant proportion of patients, but it is unlikely to replace biopsy procedures in the near future. PET-CT without contrast allows evaluating the extension of vascular involvement; however, it cannot accurately analyze the vascular wall. The intensity of vascular inflammation, moreover, can help in the differential diagnosis and it can be a useful tool for monitoring response to therapy.

As described by Kumar et al (2012)., the correlation between the inflammatory status and FDG uptake also allows to use PET in follow up, for evaluating response to LVV therapy, and to detect possible flares before complications arise.

In a prospective study by Blockmans et al. (2006) involving 35 patients (CAO) with GCA, a significant decrease in vascular FDG uptake at 3 months indicated a potential future response to treatment.

As with previous reports, we confirm the lower diagnostic accuracy in patients on immunosuppressive therapy. We chose a cut off of 5 mg/day of prednisone for a week because this dose does not seem to interfere with SUV, but it is often impractical to not treat a severe vasculitis before obtaining a PET scan.

Even our data, in agreement with what is reported in the literature, do not allow to express an opinion on a possible involvement of cerebral vessels given the high uptake of FDG in brain tissue.

Qui Lin et al. (2012) reviewed the literature on the use of PET in the diagnosis of FUO, and it was found that PET's mean sensitivity was 80-90% and specificity was 88-90%. FDG PET scans were examined in various cases. A definitive diagnosis was made in 50% of cases and 20% of cases were related to inflammatory processes of

the great vessels. Therefore, Yang et al. (2012) confirmed the superiority of PET among the various diagnostic techniques used in the diagnosis of FUO, with an excellent cost benefit profile, the possibility of reducing the number of surveys and the duration of hospitalization.

In our study, the use of PET in patients with FUO has allowed us to make a diagnosis in 80% of cases, of which 70% was a vasculitis.

Conclusion

^{18}F-FDG PET/CT (PET) is a sensitive and specific imaging tool for large vessel vasculitis (LVV) and FUO; it increases the overall diagnostic accuracy and has an impact on the clinical management in a significant proportion of patients for several reasons. FUO might be caused by a vasculitis. PET is a one-shot diagnostic method (cost saving) as reported by Becerra et al. (2012). Its diagnostic accuracy precludes the need for arterial biopsy, and instead an easy semi-quantitative analysis can be used for the right diagnosis of vasculitis. Finally, PET is a good tool for the diagnosis of LVV, but also for therapy monitoring and follow up.

However, since this method still encounters some resistance to be used as the gold standard in the diagnostic guidelines of FUO, further studies are needed to confirm the specificity, accuracy and sensitivity as well as the cost benefit analysis in the diagnosis of vasculitis.

Disclosures

None

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