Original Article

\textbf{\textsuperscript{18}F-FDG PET/CT for the detection of large vessel vasculitis in patients with polymyalgia rheumatica}

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\section*{A R T I C L E  I N F O}

\textbf{Article history:}
Received 23 April 2015
Accepted 27 May 2015
Available online 6 July 2015

\textbf{Keywords:}
Polymyalgia rheumatica
Large vessel vasculitis
Aortitis
Giant cell arteritis
\textsuperscript{18}F-FDG PET/CT
Positron emission tomography

\section*{A B S T R A C T}

\textbf{Purpose:} Polymyalgia rheumatica (PMR) may present together with large vessel vasculitis (LVV), and frequently requires a more intensive therapy. The aim of the study was to evaluate the impact of \textsuperscript{18}F-FDG PET/CT in the diagnosis and management of LVV associated to PMR.

\textbf{Material and methods:} This prospective study included 40 consecutive patients (27 women/13 men, 68.10 ± 10.27 years) with PMR and suspicion of associated LVV submitted for \textsuperscript{18}F-FDG PET/CT. A PET/CT scan was obtained 180 min after \textsuperscript{18}F-FDG intravenous injection. A visual analysis was performed on the images. Five vascular regions were evaluated: supra-aortic trunks (SAT), thoracic aorta (TA), abdominal aorta (AA), iliac arteries (IA), and femoral/tibioperoneal arteries (FTA). The intensity of uptake was graded from 0 to 3. A final diagnosis of LVV was established in 26/40 patients (65%).

\textbf{Results:} In the 26 patients with a diagnosis of LVV, the highest intensity of \textsuperscript{18}F-FDG uptake was observed in the TA, SAT, and FTA. All of these patients showed uptake at the TA, with grade 2 and 3 in most cases. In 4 of the 14 patients without LVV, no uptake was observed in any vascular region, and in the other 10 patients only a grade 1 uptake was observed in 1 or to 2 territories. Out of the 20 treated LVV patients, \textsuperscript{18}F-FDG PET/CT led to a therapeutic change in 17 (85%).

\textbf{Conclusion:} \textsuperscript{18}F-FDG PET/CT is useful in identifying patients with LVV associated to PMR. The detection of vascular inflammation had an important impact, and led to a change of treatment in a high percentage of patients with LVV.

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\section*{18F-FDG PET/TAC en pacientes con polimialgia reumática y sospecha de vasculitis de grandes vasos asociada}

\textbf{R E S U M E N}

\textbf{Objetivo:} La polimialgia reumática (PMR) puede presentarse asociada a vasculitis de grandes vasos (VGV), necesitando frecuentemente una intensificación del tratamiento. Nuestro objetivo fue evaluar el impacto de la \textsuperscript{18}F-FDG PET/TAC en el diagnóstico y tratamiento de VGV asociada a PMR.

\textbf{Material y métodos:} Este estudio prospectivo incluyó 40 pacientes consecutivos (27 mujeres/13 hombres, 68.10 ± 10.27 años) con PMR y sospecha de VGV asociada evaluados con \textsuperscript{18}F-FDG PET/TAC. Los estudios PET/TAC fueron obtenidos 180 minutos después de la inyección intravenosa de \textsuperscript{18}F-FDG. Se realizó un análisis visual de la intensidad de captación (0–3) en troncos supraaórticos (TSA), aorta torácica (AT), aorta abdominal (AA), arterias ilíacas (AI) y arterias femoro/tibioperoneales (AFT). Se estableció un diagnóstico final de VGV en 26/40 pacientes (65%).

\textbf{Resultados:} En los 26 pacientes con diagnóstico de VGV la mayor intensidad de captación de \textsuperscript{18}F-FDG se objetivó en AT, TSA y AFT. En todos ellos se observó captación en la AT, principalmente grado 2 y 3. En 4 de los 14 sin VGV no se visualizó captación en ninguna región vascular y en los otros 10 solo se observó captación grado 1 en uno o 2 territorios. De los 20 pacientes con VGV previamente tratados, la \textsuperscript{18}F-FDG PET/TAC motivó un cambio terapéutico en 17 (85%).

\textbf{Conclusiones:} La \textsuperscript{18}F-FDG PET/TAC fue una herramienta útil para identificar pacientes con VGV asociada a PMR. La detección de inflamación vascular tuvo un importante impacto, motivando un cambio de tratamiento en un alto porcentaje de los pacientes con VGV.

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http://dx.doi.org/10.1016/j.remn.2015.05.011
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**Introduction**

Polymyalgia rheumatica (PMR) is a relatively common inflammatory rheumatic disease characterized by aches and morning stiffness in the neck, shoulders and pelvis girdles affecting older people. PMR frequently occurs as an isolated condition, showing in general a rapid response to low-dose steroid therapy, but it may present concomitantly with large vessels vasculitis (LVV)\(^1\)-\(^5\). LVV is due to a leukocytic infiltration of the vessel walls in large arteries, especially the aorta and its main branches, and increases the risk of vascular complications such as aneurysms, stenosis, and stroke\(^6\)-\(^8\). An association between LVV and PMR has been previously described and several authors consider both processes as part of the same disease\(^2\),\(^3\),\(^9\),\(^10\). Thus, a positive temporal biopsy for giant cell arteritis (GCA) was found in 20% of the patients with PMR and no symptoms of GCA\(^11\),\(^12\), and, on the other hand, a polymyalgic symptomatology has been found in 40–50% of the patients with GCA\(^3\),\(^13\),\(^14\). The lack of improvement after steroid therapy, the presence of non-specific symptoms (fatigue, fever, weight loss, night sweats), and a prolonged increased C-reactive protein level or erythrocyte sedimentation rate raises the suspicion of an associated LVV which is often overlooked. In order to prevent irreversible tissue damage of the vessel walls, an early diagnosis and treatment and a close monitoring of these patients is mandatory. However, the diagnosis of an associated LVV remains a challenge. Temporal artery biopsy is frequently negative due to the segmental nature of this inflammation, the likelihood of exclusive extracranial involvement or not sufficient sample for a reliable histopathological analysis. The major limitation of the structural imaging techniques (Doppler ultrasound, magnetic resonance imaging and computerized tomography) is the low sensitivity for the detection of the early inflammatory involvement as they only show the late anatomical changes such as stenosis and aneurysms\(^15\). In addition, they do not provide accurate information on the exact extent and intensity of the disease.

Positron emission tomography (PET) is a powerful tool that provides highly sensitive functional imaging at a molecular level, revealing one of the important pathophysiological processes underlying inflammation\(^16\). Therefore, the advantage of \(^18\)F-FDG PET/CT imaging is that vessel wall inflammation can be detected early during the development of the disease before morphological changes are seen\(^1\). Additionally, it allows the evaluation of the whole body in a single examination and provides the anatomical information due to the CT component.

In previous studies, \(^18\)F-FDG PET/CT has widely proved to be useful in the early diagnosis, the assessment of the extent of LVV and the monitoring of treatment response\(^17\)-\(^25\). However, there are only a few published work focused on the vascular inflammation using \(^18\)F-FDG PET/CT in patients with PMR, and none of them specifically involving therapy, which is a relevant issue. In this context, we have designed this study with the aim of assessing the impact of \(^18\)F-FDG PET/CT in the diagnosis and management of patients with LVV associated to PMR.

**Materials and methods**

**Patients**

This prospective study included 40 consecutive patients (27 women and 13 men, mean age: 68.10 ± 10.27 years) with PMR and suspicion of associated LVV submitted for \(^18\)F-FDG PET/CT scan between May 2013 and January 2015. The suspicion of associated LVV rose from the clinical data in 33 out of the 40 patients (including abnormal temporal artery on physical examination, headache of recent onset, visual symptoms, constitutional syndrome, fever, intermittent claudication of the lower limbs, lack of treatment response) and/or biochemical data in 34 patients (based on increased erythrocyte sedimentation rate and/or C-reactive protein).

The mean erythrocyte sedimentation rate (ESR) was 39.03 ± 26.07 mm/h (normal 1–20 mm/h) and the mean plasma C-reactive protein (CRP) level was 1.39 ± 1.54 mg/dl (normal <0.5 mg/dl).

The final diagnosis was established by the combination of clinical and biochemical data, treatment response, \(^18\)F-FDG PET/CT initial findings and follow up, temporal artery biopsy, and conventional radiological imaging. According to these criteria, the patients were classified into two groups: patients with a diagnosis of LVV associated to PMR (26 out of the 40 patients, 65%) and patients without LVV (14 out of the 40, 35%). There were no significant differences between both groups of patients regarding sex, age, ESR or CRP (Table 1). The final diagnosis of the 14 patients without LVV was atypical PMR (5 patients), ankylosing spondylitis (2 patients), rheumatoid arthritis (2 patients), panarteritis nodosa (1 patient) and in 4 patients a definitive diagnosis has not been established.

Twenty-eight out of the 40 patients (70%) were on treatment during \(^18\)F-FDG PET/CT scan: 20 with a final diagnosis of LVV (19 were receiving steroids and 1 steroids plus methotrexate) and 8 without LVV (6 were receiving steroids and 2 steroids plus methotrexate).

**\(^18\)F-FDG PET/CT acquisition**

Patients fasted for at least 6 h before the examination. \(^18\)F-FDG PET/CT scan was obtained 180° after intravenous injection of 7 MBq/kg of \(^18\)F-FDG. The serum glucose level was below 160 mg/dl in all patients (mean value: 110.51 ± 21.45 mg/dl). Whole body scan including lower limbs was acquired using a Biograph LSO Pico 3D from Siemens Healthcare Molecular Imaging (Hoffman Estates, IL, USA). A low-dose CT scan (50 mAs, 130 kv) for attenuation correction and anatomic localization was first obtained. Then, a PET scan was acquired (250 s bed position). Iterative reconstruction was performed using the ordered subset expectation maximization (OSEM) algorithm applying two iterations and eight subsets.

**Analysis of \(^18\)F-FDG PET/CT images**

Two experienced nuclear medicine specialists blinded to clinical, radiological and laboratory data performed a visual analysis of \(^18\)F-FDG PET/CT images by consensus.

Five vascular regions were analyzed: supra-aortic trunks (SAT), thoracic aorta (TA), abdominal aorta (AA), iliac arteries (IA) and femoral/tibioperoneal arteries (FTA). The intensity of \(^18\)F-FDG uptake in each region was graded from 0 to 3 in comparison to the liver uptake (0: no uptake, 1: lower than liver uptake, 2: similar to liver uptake, and 3: higher than liver uptake). Vasculitis was reported when a linear uptake along the vessel wall showing a grade 2 or 3 intensity in at least one vascular region.

The CT images were used to anatomical localization and also to evaluate the presence of vessel calcification and to compare the regional distribution of calcification and FDG uptake.

The results obtained for patients with and without a final diagnosis of LVV were compared. In addition, the therapeutic management after \(^18\)F-FDG PET/CT of the patients with a diagnosis of LVV was evaluated.

**Statistical analysis**

All data are expressed as mean ± standard deviation (SD). The p value was calculated using the Mann–Whitney U-test for
nonparametric data and the chi-square using AnalystSoft Biostat Version 2009 for Windows (AnalystSoft Inc., Vancouver, Canada). Statistical significance was established at p values lower than 0.05. The study was approved by the hospital ethical committee and all patients signed a written informed consent.

Results

Patients with a final diagnosis of LVV

An overall approach to the results obtained in patients with a final diagnosis of LVV according to the intensity of 18F-FDG uptake for the different vascular regions is shown in Table 2, while in Table 3 a more detailed information for each patient is included.

<table>
<thead>
<tr>
<th>Grade of 18F-FDG uptake</th>
<th>SAT</th>
<th>TA</th>
<th>AA</th>
<th>IA</th>
<th>FTA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>6</td>
<td>2</td>
<td>14</td>
<td>5</td>
<td>34</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>14</td>
<td>3</td>
<td>1</td>
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</tr>
<tr>
<td>2</td>
<td>2</td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>4</td>
<td>16</td>
</tr>
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</table>


18F-FDG uptake was observed at the SAT in 16 patients (61.54%), and the intensity of uptake was grade 1 in 6 patients, grade 2 in 8 patients and grade 3 in 2 patients.

With regard to the TA region, all 26 patients (100%) with a final diagnosis of LVV showed 18F-FDG uptake. The intensity of uptake was grade 3 in 10 patients (38.46%) and grade 2 in 14 patients (53.85%). In 2 patients (7.69%) the intensity of the TA was grade 1. In these 2 patients (no. 25 and 26) the greater intensity of uptake, grade 2, was observed in the FTA.

The AA showed 18F-FDG uptake grade 1 in 14 patients and grade 2 in 3 patients. The IA showed 18F-FDG uptake grade 1 in 5 patients and grade 2 in 1 patient. None of the patients showed a grade 3 uptake at the AA or IA.

Finally, 14 patients showed 18F-FDG uptake at the FTA (grade 1 in 6 patients, grade 2 in 4 patients and grade 3 in 4 patients). Seven of these 14 patients had symptomatology in the lower extremities (3 patients had a grade 1 uptake, 2 patients a grade 2 and 2 patients a grade 3) and the other 7 presented no symptoms.

The intensity of uptake at the FTA was lower than TA in 7 patients, equal in 3 and higher in 4 patients (Fig. 1). In 3 of these 4 patients with a higher uptake at the FTA compared to the TA the predominant symptomatology was in the lower limbs.

Three patients (no. 5, 9 and 20) showed 18F-FDG uptake in all vascular regions evaluated, the highest intensity of uptake being at the TA, the SAT and the FTA.

Patients without LVV

Four of the 14 patients without LVV (28.57%) showed no uptake in the 5 evaluated vascular regions.

In the remaining 10 patients (71.43%) only a grade 1 uptake was observed in 1 or 2 vascular regions: in 9 patients the uptake was detected at the TA (lineal pattern in 7 and patchy in 2), in 3 at the SAT, in 3 at the AA and, finally, in 3 at the FTA. No patient showed vascular uptake grade 2 or 3 (Tables 4 and 5).

Impact of 18F-FDG PET/CT in the management and follow-up of patients with a diagnosis of LVV

Twenty out of the 26 patients with a diagnosis of LVV were on treatment at the time of PET/CT examination and six were not treated (Fig. 2).

18F-FDG PET/CT findings led to a change of therapy in 17 out of these 20 previously treated patients (85%). In 6 of them the steroid dose was increased and in 11 the steroid dose was increased and/or

Table 4

<table>
<thead>
<tr>
<th>Grade of 18F-FDG uptake</th>
<th>SAT</th>
<th>TA</th>
<th>AA</th>
<th>IA</th>
<th>FTA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>11</td>
<td>5</td>
<td>11</td>
<td>14</td>
<td>11</td>
<td>52</td>
</tr>
<tr>
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<td>3</td>
<td>9</td>
<td>3</td>
<td>–</td>
<td>3</td>
<td>18</td>
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<td>2</td>
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methotrexate or tocilizumab was added. In the other 3 patients (15%) no changes were made on the previously established steroid therapy. On the other hand, in all of the 6 no previously treated patients at the time of PET/CT a steroid and/or methotrexate therapy was started or reintroduced (Fig. 3).

With regard to outcome, 19 out of the 26 patients (73.08%) with LVV had a good clinical and laboratory response and in 8 of them a new PET/CT performed to monitor treatment response showed a decrease of $^{18}$F-FDG uptake. In 6 patients (23.08%) a poor response or worsening was observed despite treatment increase and the follow-up PET/CT showed an increase in the vascular uptake. Finally, 1 patient (3.84%) in whom the treatment was not changed suffered a worsening prompting increased treatment.

**Discussion**

The first time vascular $^{18}$F-FDG uptake in patients with PMR was reported in 1999. $^{18}$F-FDG uptake was observed in the thoracic vessels (4 out of the 5 patients) and the upper leg vessels (3 out of the 5 patients). Since then, several authors have also reported vascular $^{18}$F-FDG uptake in patients with PMR. In a study including 25 patients, a vascular uptake was observed in 75% of the cases. The sensitivity for the TA was 56%, the specificity was 98% and the positive predictive value 93%. The uptake in the leg arteries was less specific (77%).

Moosig et al. studied 13 untreated patients with active PMR, using both a visual and a quantitative analysis. They described
increased $^{18}$F-FDG uptake in the aorta and its main branches in 12 of these patients (92.3%), with a strong correlation with the inflammatory parameters and a significant decrease of uptake during the follow-up.\textsuperscript{4}

Vascular involvement, especially in the subclavian arteries, was reported in another article in 31% of the patients with isolated PMR and in whom the temporal artery biopsy was negative. The authors noted that the vascular uptake was less frequent and less intense in comparison with patients with GCA and decreased during follow-up in most patients.\textsuperscript{19}

In our study, 65% of the patients were diagnosed of LVV. The discrepancies between our results and the published articles according to the percentage of patients with PMR that showed vascular involvement can be explained by a combination of several factors such as the heterogeneity of the population regarding age, sex, inclusion criteria, treatment, etc. There are also some other technical aspects that should be taken into account such as the different acquisition protocols and criteria for interpretation of PET/CT images used. Thus, we use a more delayed acquisition in comparison to that applied for oncologic purposes as it has demonstrated a better visualization of the vessel wall uptake due to the decrease of the blood pool activity and the increase in the lesion/background ratio.\textsuperscript{21} An increased $^{18}$F-FDG uptake time was also recommended by others.\textsuperscript{5}

Depending on the different vascular regions evaluated the incidence of vascular involvement was very different. It should be highlighted that the TA was the most frequently involved region and it also showed the most intense $^{18}$F-FDG uptake (grade 2 or 3 in more than 90% of the cases). This is in accordance with previous studies, both for GCA and PMR, who reported the TA as the most frequent and specific site of inflammation.\textsuperscript{2,21}

The SAT was the second most frequently involved vascular region, and grade 2 the predominant intensity of uptake. The percentage of AA involvement was similar to the SAT, although in this case the intensity was much lower. The FTA showed $^{18}$F-FDG uptake in more than half of the patients. Finally, the IA were the less involved arteries and in almost all cases, the intensity of the uptake was mild and limited to its initial portion. Our results are not in accordance with those of a study published in 2012 including 14 untreated patients with active PMR and 17 controls. In the cited study, although a significantly higher vascular uptake was found in patients with PMR compared with controls, the intensity of uptake was very mild in most of the patients and only 2 showed intense $^{18}$F-FDG uptake in the aorta and subclavian arteries.\textsuperscript{20} However, it should be considered that the two populations evaluated are very different (patients with PMR and a high suspicion of LVV based on clinical and laboratory data in the present study vs. asymptomatic patients for arteritis) regarding the pretest probability of vascular inflammation.

An important aspect is the association between the PET/CT findings and symptomatology. Thus, regarding the involvement of the leg arteries and, as we already noted, more than a half of the patients (14 out of 26) with a diagnosis of LVV showed $^{18}$F-FDG uptake at the FTA. The intensity of the uptake was predominantly grade 2 or 3. Interestingly, only half of these 14 patients had symptomatology in the lower extremities complaining of pain and intermittent claudication. The other 7 patients were asymptomatic for the legs, in spite of a high intensity of $^{18}$F-FDG uptake (grade 3) in some cases. In 4 patients the uptake at the FTA was more intense than in the TA, in 3 of them the predominant symptoms involved the lower extremities. In summary, the vascular uptake in the lower extremities explained the symptomatology in some patients although an intense $^{18}$F-FDG uptake in the FTA was not always accompanied by specific symptoms.

Table 5

$^{18}$F-FDG uptake in each of the 14 patients with a final diagnosis of no large vessel vasculitis according to the different vascular regions evaluated.

<table>
<thead>
<tr>
<th>No. patient</th>
<th>Intensity of $^{18}$F-FDG uptake</th>
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<tr>
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<td>SAT</td>
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Patchy uptake.
Another interesting issue that deserves a detailed analysis is the result obtained in the group of patients without LVV. Thus, a grade 1 uptake was seen in more than 70% of these patients within a maximum of 1 or 2 vascular regions, more frequently at the TA, followed by the SAT, the AA and the FTA. Most authors agree that a mild vascular $^{18}$F-FDG uptake is seen in controls and is not indicative of vascular inflammatory involvement, and this could be closely related with the time of acquisition and, in this sense, semiquantitative analysis could help to a more objective interpretation. A mild $^{18}$F-FDG uptake in the leg arteries has been described in more than 26% of the controls. This uptake is considered less specific for vasculitis and has been attributed to atherosclerosis, especially when a patchy pattern was observed. In this sense, the morphological information provided by the CT component of the PET/CT is important establishing the presence of calcifications within the arterial wall.

As in most of the published work, a high percentage of our patients were under therapy with steroids or other immunosuppressive drugs at the moment of the PET/CT scan. It has been reported that a previous therapy causes a decrease in the intensity of the vessel wall uptake that should be taken into account when interpreting the PET/CT findings. However, despite a previous treatment in these patients, the technique proved to be useful for the patients’ management. A study published in 2008 reported that 3 out of 8 patients (37.5%) with PMR and low-dose steroid-resistant were diagnosed of LVV by PET.

The reports on the impact of $^{18}$F-FDG PET/CT on the clinical management of patients with LVV are scarce. Thus, Fuchs et al. published an interesting study performed in patients with and without immunosuppressive therapy and suspicion of LVV, also using a visual analysis of the vascular uptake in comparison to the liver uptake. The addition of $^{18}$F-FDG PET/CT changed the treatment recommendation in more than 20% of patients both with and without immunosuppressive therapy. However, to the best of our knowledge, there are no published studies specifically addressed to evaluate the impact in the management of patients with PMR and suspicion of LVV. Our results prove the strong influence of $^{18}$F-FDG PET/CT findings in the therapeutic approach of the patients with vascular inflammation as it prompted an intensification in the treatment in a high percentage of the cases. During the outcome, a good clinical and laboratory response and a decrease on $^{18}$F-FDG uptake was noted in more than 70% of these patients. However, a small number of patients showed a clinical worsening and increased $^{18}$F-FDG uptake despite treatment intensification. It should be emphasized that we have not found significant differences between patients with a good or a poor response to treatment according to symptomatology, ESR, CRP level or PET/CT findings. Therefore, PET/CT was not able to predict the treatment response in these patients. In this sense, it has been previously reported both in patients with GCA and PMR that $^{18}$F-FDG PET/CT is not a good predictor of relapse and is not able to identify those patients who will require a longer steroid therapy.

The main limitations of this study, as it happens in most of these kinds of studies, are related to the absence of a gold standard for the diagnosis of LVV and the lack of a histological confirmation. Also, the use of the PET/CT itself as a criterion for the diagnosis and for the therapeutic decision obviously may introduce a bias.

In conclusion, our results confirmed that $^{18}$F-FDG PET/CT was a useful tool in identifying patients with LVV associated to PMR, providing valuable information on the extent and intensity of the vascular involvement and allowing a reliable follow-up of the patients. The detection of vascular inflammation by $^{18}$F-FDG PET/CT had an important impact and led to a change of treatment in a high percentage of the patients with a diagnosis of LVV.

Conflict of interest

The authors declare that they have no conflict of interest.

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