Special collaboration

Use of positron emission tomography (PET) for the diagnosis of large-vessel vasculitis

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A B S T R A C T

The term vasculitis encompasses a heterogeneous group of diseases that share the presence of inflammatory infiltrates in the vascular wall. The diagnosis of large-vessel vasculitis is often a challenge because the presenting clinical features are nonspecific in many cases and they are often shared by different types of autoimmune and inflammatory diseases including other systemic vasculitides. Moreover, the pathogenesis of large-vessel vasculitis is not fully understood. Nevertheless, the advent of new imaging techniques has constituted a major breakthrough to establish an early diagnosis and a promising tool to monitor the follow-up of patients with largevessel vasculitis. This is the case of the molecular imaging with the combination of positron emission tomography with computed tomography (PET/CT) using different radiotracers, especially the 18F-fluorodeoxyglucose (18F-FDG). In this review we have focused on the contribution of 18F-FDG PET in the diagnosis of large-vessel vasculitis.

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Utilización de la tomografía por emisión de positrones (PET) para el diagnóstico de vasculitis de vaso grande

R E S U M E N

El término vasculitis engloba un heterogéneo grupo de enfermedades que tienen en común la presencia de un infiltrado inflamatorio en la pared vascular. El diagnóstico de las vasculitis de vaso grande es a menudo difícil debido a que pueden comenzar con una sintomatología inespecífica que también puede aparecer en otros tipos de enfermedades autoinmunes e inflamatorias, incluyendo otras vasculitides sistémicas. Además, la patogenia de las vasculitis de vaso grande no se conoce en su totalidad. Sin embargo, el desarrollo de nuevas técnicas de imagen constituye un gran avance para establecer un diagnóstico precoz y son una herramienta prometedora para el seguimiento de las vasculitis de vaso grande. Este es el caso de la imagen molecular obtenida de la combinación de la tomografía por emisión de positrones con la tomografía computarizada (PET/TAC) utilizando diferentes radiotrazadores, especialmente la 18F-fluorodeoxiglicerosa (18F-FDG). En esta revisión nos hemos centrado en la contribución del 18F-FDG PET en el diagnóstico de las vasculitis de vaso grande.

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Introduction

Otto Warburg showed that cancer cells had an increased aerobic glycolysis. Fluorodeoxyglucose (FDG) is usually used to trace glucose metabolism. Most tumor cells are FDG-avid. Because of that, the PET/CT has improved the diagnostic accuracy in oncology. Moreover, FDG-uptake use is not only limited to cancer but it may be also utilized in different conditions associated with inflammation.

In this regard, elevated FDG-uptake by activated macrophages and by newly formed granulation tissue was demonstrated by Kubota et al.2 In addition, numerous cytokines and growth factors act on the inflammatory cells and transform them into activated cells. This process results in an increase in the expression and the affinity of the glucose transporters, mainly GLUT-1 and GLUT-3, and greater production of glycolytic enzymes such as hexokinase. It also results in an increase of 18F-FDG uptake. Nevertheless, 18F-FDG PET alone does not provide a good spatial resolution. For this reason, 18F-FDG PET is usually complemented by CT (18F-FDG PET/CT), and a combination of precise anatomic localization and functional status of metabolically active lesions is achieved overlaying the two images in a single image.1,4

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Usefulness of molecular imaging with PET in rheumatology

Early diagnosis and effective therapy can improve the outcome of many rheumatic diseases. In the last decade a number of studies have emphasized the usefulness of PET in the diagnosis of rheumatic diseases such as systemic vasculitis, polymyalgia rheumatica, sarcoidosis, rheumatoid arthritis, idiopathic juvenile arthritis, and systemic lupus erythematosus. In this article we will focus on the use PET in large-vessel vasculitis.

Large-vessel vasculitis

18F-FDG PET/CT plays an important role as a non-invasive tool for the diagnosis and management of patients with large-vessel vasculitis by providing a metabolic functional image of the vessel wall inflammation before structural changes can be observed. This technique is especially helpful in atypical presentations of vasculitis. Aortitis is the inflammation of aortic wall and it can be idiopathic or associated with a cluster of large-vessel infectious and non-infectious diseases. In turn, non-infectious aortitis may be of unknown etiology or associated with well-defined entities. The most common well-characterized underlying causes of non-infectious aortitis are giant cell arteritis (GCA) and Takayasu arteritis (TakA), which are primary large-vessel vasculitides. However, non-infectious aortitis is often an underrecognized condition usually presenting with non-specific symptoms. For this reason, a high degree of clinical suspicion is required to make a diagnosis of aortitis. The presenting symptoms are often non-specific and include fever, asthenia and abdominal or back pain along with raised erythrocyte sedimentation rate (ESR) or serum C-reactive protein (CRP) levels. Early diagnosis is very important to prevent the development of serious complications such as aneurysms, dissection and rupture of the aorta.

The use of 18F-FDG PET/CT has improved the accuracy of diagnosis and management of large-vessel vasculitis. According to data from different studies, 18F-FDG sensitivity to make an early detection of active arterial inflammation ranges between 60% and 92%, whereas the specificity ranges between 88% and 100%. In this sense, we reported 32 cases diagnosed with non-infectious aortitis in our center in a 4-year period. Thirty-one of them were diagnosed with aortitis by a positive 18F-FDG uptake in PET/CT. In our series, to improve technique performance, all patients fasted for at least 6 h before the examination. The serum glucose level was lower than 160 mg/dL in all patients. Whole-body FDG-PET/CT was acquired 180 min after injection of 7 MBq/kg of 18F-FDG, using a Biograph LSO Pico 3D from Siemens Healthcare Molecular Imaging (Hoffman Estates, Illinois, USA). A low dose CT scan for attenuation correction and anatomic localization was first obtained, followed by a PET scan (acquiring 250 s/bed position). Images were reconstructed using the ordered subsets-expectation maximization (OSEM) algorithm (2 iterations, 8 subsets). Images were visually evaluated by two experienced nuclear medicine specialists according to the intensity of the 18F-FDG uptake by the vessel wall at the supraaortic trunks, thoracic aorta, abdominal aorta, iliac arteries and femoral/tibioperoneal arteries. However, glucose is not only stored in the vasculitic vessels but also in atheroma plaques, which obviously reduces the specificity of the test, although in the thoracic aorta the intensity and pattern of FDG-uptake enables differentiation by the use of the Meller visual scale, that compares the vascular FDG-uptake with the accumulation thereof in the liver, demonstrating its validity to assess the degree of inflammation and the activity of the disease.

Giant cell arteritis

Giant cell arteritis (GCA) is a vasculitis of large and medium sized arteries that affects people over 50 years. This vasculitis is common in Europe and North America and is characterized by the granulomatous involvement of the aorta with predilection for the involvement of the extracranial branches of the carotid artery. A serious complication of GCA is the irreversible visual loss due to ischemic optic neuropathy. Aortitis may also occur as well as the development of aortic aneurysms. In this regard, the use of new imaging techniques over the past 20 years has disclosed that extracranial large vessel involvement in GCA is more common than initially thought. The “gold standard” for confirmation of the diagnosis of GCA is a biopsy of the temporal artery showing an infiltrate of mononuclear cells and the presence of giant multinucleated cells. However, a negative temporal artery biopsy does not preclude the diagnosis of GCA.

Several studies have shown an abnormal production of pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-18, tumor necrosis factor-α (TNF-α), or interferon-γ in inflamed arterial walls of patients with GCA. Prieto-González et al., observed that FDG-uptake by large vessels, including aorta, has a high sensitivity and specificity for the diagnosis of GCA. Moreover, they showed that the maximal standardized uptake value (SUVM) correlated with acute phase reactants and serum IL-6 levels. However, PET/CT scan is not considered a routine diagnostic tool in the diagnosis of GCA. This technique is generally indicated in cases with atypical presentation, in individuals with nonspecific signs and symptoms, in relatively young patients or in those cases with typical cranial manifestation of GCA in whom a temporal artery biopsy yielded negative results.

However, 18F-FDG uptake is not specific for vasculitis and it does not allow the evaluation of temporal arteries owing to its special resolution and physiologic uptake by the brain and soft tissues, although the most recently introduced PET/CT cameras claim a 2.5 mm spatial resolution for the PET component under optimal conditions, expecting that pathologic 18F-FDG uptake in temporal arteritis may be found. 18F-FDG PET has been shown to be sensitive for extracranial vasculitis but not for intracranial vasculitis on account of its poor spatial resolution.

A meta-analysis on the usefulness of 18F-FDG PET in the diagnosis of GCA revealed a pooled sensitivity of 80% and a specificity of 89%. 18F-FDG PET reveals abnormal uptake in the aortic arch or large thoracic arteries in more than half of affected patients. On the other hand, 18F-FDG PET provides good results for the assessment of the degree of disease extension, which allows all the large-sized arteries to be studied in a single scan, showing more affected regions than other imaging techniques, and providing more precise evaluation of aortic involvement. Fig. 1 shows the case of a woman diagnosed with GCA who developed an aneurysm in the ascending aorta. Blockmans et al. assessed FDG-uptake in the different vascular beds and in the large joints from a series of 35 patients with GCA at diagnosis, during steroid treatment and at relapse, observing that FDG-uptake in the large-vessels was a sensitive marker for GCA, although it was not useful to discriminate the patients with relapses from the remaining patients without relapses of the vasculitis. The same group of authors highlighted that in a series of 46 patients with biopsy-proven GCA the increased FDG-uptake in the aorta predisposed to develop thoracic aortic dilatation.

Several criteria have been proposed to establish a qualitative assessment of FDG-PET in the detection of large vessels involvement in GCA. They range from increased circumferential 18F-FDG uptake in a segment of the arterial wall to equal or more intense vascular wall uptake than liver uptake. Recently, Puppo et al. performed a systematic review, including a total of 442 patients...
with GCA, and 525 controls to analyze the different qualitative and semiquantitative methods for assessing the presence and grading the severity of GCA-related vascular inflammation on 18F-FDG PET. These authors indicate that the qualitative analysis of 18F-FDG uptake is the most widely accepted method for assessing the presence and grading the activity of GCA-related vascular inflammation on 18F-FDG PET. In addition, they observed that qualitative methods are more specific than the semiquantitative procedures. On the other hand, the same group suggested that the normalization of the arterial wall uptake to the background activity of venous blood pool may provide a good reference to assess vascular inflammation. Lensen et al. evaluated the interobserver agreement and diagnostic accuracy of 18F-FDG PET for the detection of large-vessel affection in GCA. They concluded that the use of a predefined standardized criteria consisting of the comparison of vascular uptake to the liver uptake reached high interobserver agreement and probably had good diagnostic accuracy for large-vessel vasculitis.

Polymyalgia rheumatica and polymyalgia-like conditions

PMR is a common disorder in people over 50 years of age from Western countries. It is more prevalent than GCA, and it may present as an isolated condition or associated with typical ischemic manifestations of GCA. PMR may also be the presenting manifestation of GCA and clinical features of PMR are present in 40–50% patients with biopsy-proven GCA. Several reports have emphasized the presence of aortitis in some cases presenting as an isolated PMR.

The diagnosis of PMR is very straightforward when typical features, such as pain in the neck, and shoulder and pelvic girdles, are present. However, the presence of atypical symptoms or a poor response to corticosteroids should be considered alarm signs for the presence of a condition mimicking this disease but different from isolated PMR. It was also the case for some of our patients diagnosed with aortitis. In these cases, the presence of atypical findings such as low back pain, pain of polymyalgia symptoms involving mainly the legs, particularly in people in the fifties and sixties, sometimes associated to mild elevation of acute phase reactants, were the alarm signs to suspect an underlying aortitis. In addition, PMR manifestations have been associated with aortitis in the setting of well-defined conditions such as sarcoidosis or ulcerative colitis. In the cases with atypical onset and with normal or discordant inflammatory analytical parameters, 18F-FDG PET/CT provided better information on the extension of the vascular involvement and in some cases it allowed us to establish the presence of a relapse of the disease. In this regard, 18F-FDG PET/CT in patients with PMR shows a pattern of abnormally increased 18F-FDG uptake in the soft tissues and ligaments around the shoulders and hips, lumbar and, sometimes, cervical spinous processes and ischial tuberosities. 18F-FDG PET/CT may also provide an alternative diagnostic procedure and will likely contribute to the early diagnosis of spondyloarthritides in PMR. Fig. 2 illustrates the findings of a patient with PMR with affection of large vessels.

Both large-vessel vasculitis and PMR may be detected, in the early onset of the disease by 18F-FDG PET/CT. Our group reported the case of a 69-year-old woman diagnosed with PMR. Prednisone yielded an improvement of PMR symptoms. However, she started to complain of asthenia, abdominal cramping and pain on the left side, weight loss and bloody diarrhea 1 year after prednisone discontinuation. At that time a colonoscopy confirmed a diagnosis of left-sided ulcerative colitis. She suffered many relapses of the ulcerative colitis that required admission and treatment with high dose of corticosteroids and azathioprine. Because of that a colectomy was performed. Four months later, she started to feel dull and achy pain in the thighs along with claudication of the lower extremities. An 18F-FDG PET/CT revealed an inflammatory process with moderate increased FDG-uptake in the thoracic aorta and markedly increased metabolism in the femoral and posterior tibial arteries on both limbs. On the other hand, our group also reported the case...
of a 56-year-old man who presented to the rheumatology outpatient clinic due to a flare of PMR. Almost 2 years before, he had been diagnosed as having isolated PMR, because of a 5-month-history of pain and achiness involving the neck, the shoulder and the pelvic girdle, as well as proximal aspects of arms and legs, along with morning stiffness and elevation of inflammatory laboratory markers (acute phase reactants). Owing to the presence of a refractory disease and the development of atypical symptoms such as fever, severe inflammatory low back pain, dull and aching pain in the thighs, claudication of the lower extremities and bad response to corticosteroids and methotrexate, an \(^{18}\)F-FDG PET/CT was performed. This technique disclosed an arteritis of large-vessel involving the ascending, arch and descending aorta and high FDG-uptake in the femoral and posterior tibial arteries of both lower limbs. Furthermore, increased metabolism was observed in the right paratracheal, retrotrochlear, subcarinal, gastrohepatic ligament, celiac and right renal hilar lymph nodes. Four lymph nodes, taken during mediastinoscopy disclosed a diagnosis of sarcoidosis.\(^{40}\) In our report on 32 patients with non-infectious aortitis, the findings of \(^{18}\)F-FDG PET/CT were crucial for the correct diagnosis of aortitis in patients presenting with PMR, mainly in those with atypical symptoms.\(^{11}\)

**Takayasu arteritis (TakA)**

TakA is a large-vessel vasculitis characterized by a chronic granulomatous, inflammatory and stenotic disease, mainly affecting the aorta and its main branches.\(^{14}\) It is more frequent in Asiatic women aged 20–40 years.\(^{14}\) Early diagnosis is important to prevent irreversible structural changes. The American College of Rheumatology established in 1990 a series of clinical, radiological and histological classification criteria for large-vessel vasculitis, with a sensitivity of 91.2% and 97.8% for TakA.\(^{51}\) These criteria are still applied nowadays. However, many patients with TakA do not meet these classification criteria as they often present with non-specific clinical signs and symptoms.\(^{52}\) The role of \(^{18}\)F-FDG PET/CT in the assessment of disease activity and progression of TakA was reviewed by Direskeneli et al.\(^{53}\) Karapolat et al. published a cross-sectional study of 22 patients with TakA and assessed the clinical disease by the combination of National Institutes of Health (NIH) criteria, Disease Extent Index-Takayasu (DEI-Tak) score, physician global assessment and \(^{18}\)F-FDG PET/CT. These authors observed that \(^{18}\)F-FDG PET/CT findings were generally consistent with the clinical disease status in patients with TakA.\(^{54}\) Moreover, these authors disclosed that the mean \(^{18}\)F-FDG PET values did not have a correlation with ESR and CRP. This fact was also described by Tombetti et al.\(^{55}\) Interestingly, the duration of the disease was shorter in \(^{18}\)F-FDG PET/CT positive patients, which may be due to long-term suppression of vascular inflammation as the result of immunosuppressive treatment.\(^{54}\)

\(^{18}\)F-FDG PET, either alone or in combination with contrast enhanced CT or MRA, has emerged as a potential tool for the initial diagnosis and assessment of disease activity of aortitis caused by TakA with a variable sensitivity ranging between 60% and 90% and a specificity between 77% and 100%. In addition, \(^{18}\)F-FDG PET/CT has proved to be useful to monitor treatment response.\(^{12,19,20,55-59}\) A meta-analysis showed that this technique has moderate value to establish TakA activity.\(^{56}\) We have assessed seven patients diagnosed with TakA who were treated with tocilizumab (TCZ). The involvement of the aorta and its main branches was verified by imaging techniques (PET/CT in five of them).\(^{14}\) Although angiography has been considered the gold standard procedure to diagnose TakA, it is an invasive tool and because of that it has been replaced by other techniques, such as angio-CT scan, MRI, ultrasonography or PET/CT.

TakA may also affect pulmonary arteries. In this regard, a study showed abnormal pulmonary perfusion scintigraphy findings in 57% of unselected patients with TakA, whereas only 21% had pulmonary symptoms.\(^{60}\) With respect to this, Addimanda et al. have suggested that although PET/CT is very sensitive to disclose active TakA, it cannot adequately visualize the pulmonary arteries and, a complementary imaging technique such as pulmonary perfusion scintigraphy, CT-angiography or magnetic resonance angiography is required to assess pulmonary artery abnormalities in TakA patients.\(^{51}\)

**Idiopathic aortitis**

Idiopathic or isolated aortitis is a disorder characterized by giant cells or lymphoplasmacytic inflammation of the aorta.\(^{52}\) Two related entities have been described: isolated idiopathic thoracic
aortitis and chronic periаortitis that encompass disorders such as idiopathic retroperitoneal fibrosis (Ormond disease), inflammatory abdominal aortic aneurysm, periаneurysmal aortitis and idiopathic isolated abdominal aortitis. Isolated aortitis usually manifests as an aneurysm of the ascending aorta and it is often disclosed during the histopathological study of the aortic wall after thoracic surgery. Nevertheless, it may also present with symptoms related to aortic inflammation. We have recently reported two patients with idiopathic aortitis. In both cases PET/CT findings were crucial to establish a diagnosis of aortitis. The first patient was a 64-year-old man with fever and dyspnea of 1 month duration. On admission the patient was febrile and wheezes were heard over both lungs. Moreover, acute phase reactants (inflammatory laboratory markers) were elevated. A temporal artery biopsy yielded negative results. Thoracic and abdominal CT-scans and CT-angiography revealed emphysematous lungs with small bullae in upper lobes and a bronchoscopic disclored slightly enlarged left paratracheal lymph nodes. The biopsy revealed reactive lymphadenitis. An 18F-FDG PET/CT showed an increased FDG-uptake in the paratracheal and hilar lymphadenopathies in the prevascular region. Furthermore, an increased FDG-uptake was also observed in the thoracic and abdominal aorta, supraaortic vessels and iliac arteries. The other patient was sent to the Rheumatology Division due to chest pain, inflammatory low back pain and a constitutional syndrome. The acute phase reactants were also raised and leukocytosis and high serum levels of creatinine and urea were also present. A body-CT scan disclosed diffuse atherosclerosis with aortocoronary calcification and an elongated aorta. A 18F-FDG PET/CT showed homogeneous and diffuse increased FDG-uptake in the thoracic aorta, supraaortic vessels and large vessels of lower limbs.

Aortitis related to other diseases

Besides the cases of sarcoidosis and ulcerative colitis that we described above, we have also found other entities in which 18F-FDG PET/CT was useful to disclose the presence of vasculitis involving the aorta and/or its major branches. In this sense, we described the case of a 71-year-old woman who had previously been diagnosed with Sjögren's syndrome. She started on corticosteroids, but she always had persistently high erythrocyte sedimentation rate (ESR) levels. An 18F-FDG PET/CT showed increased vascular uptake with a typical pattern suggestive of aortitis. We also reported the case of a 79-year-old woman with Sjögren's syndrome. This patient also had persistently elevated ESR and anemia. 18F-FDG PET/CT showed an increased FDG-uptake in the thoracic aortic wall. We also described a 45-year-old man with psoriatic arthritis who was in clinical remission following anti-tumor necrosis factor-monoclonal antibody-infliximab therapy. However, the patient suffered a stroke and began with wandering body pains, as well as a burning sensation located in the lateral region of the left lower extremities. For this reason, an 18F-FDG PET/CT was performed. This technique disclosed abnormally increased FDG-uptake in the ascending and descending thoracic aorta, aortic arch and supraaortic vessels.

Conclusion

Large arteries are commonly involved in patients with large-vessel vasculitis. GCA and TakA are the main primary large-vessel systemic vasculitides involving the aorta and its major branches. Classically the diagnosis of these two large-vessel vasculitis has been based on the presence of typical clinical features along with the histopathologic confirmation by a temporal artery biopsy in cases of GCA or by the presence of abnormal angiography findings in those with TakA. Nevertheless, imaging techniques have emerged as a useful tool for the diagnosis, in particular in those presenting with atypical manifestations, and the follow-up of patients with large-vessel vasculitis. Among them, 18F-FDG PET/CT has shown promising results in the study of large-vessel vasculitis, in particular in patients with idiopathic aortitis and to establish the presence of aortitis in individuals with well-defined inflammatory conditions who show non-specific symptoms or clinical manifestations unrelated to these conditions. Regardless of the etiology, 18F-FDG PET/CT is useful for the diagnosis, assessment of the degree of activity, extension and follow-up of patients with aortitis.

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Conflict of interest

The authors declare no conflict of interest.

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