Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

F-18-fluorodeoxyglucose positron emission tomography in diagnosis and follow-up of patients with different types of vasculitis

C.P. Bleeker-Rovers[1,2*], S.J.H. Bredie[1], J.W.M. van der Meer[1#], F.H.M. Corstens[2], W.J.G. Oyen[2]

Departments of [1]Internal Medicine and [2]Nuclear Medicine, University Medical Centre St Radboud, PO Box 9101, 6500 HB Nijmegen, the Netherlands, tel.: +31 (0)24-366 50 49, fax: +31 (0)24-361 89 42, e-mail: c.bleeker-rovers@nucmed.umcn.nl, * corresponding author

ABSTRACT

Background: F-18-fluorodeoxyglucose (FDG) accumulates in inflammatory cells due to an increased metabolic rate. Therefore, FDG positron emission tomography (PET) represents a promising imaging technique in patients with vasculitis. The aim of this study was to assess the value of FDG PET in the diagnosis of different types of vasculitis.

Methods: The results of FDG PET performed because of suspected vasculitis or fever of unknown origin with results indicating vasculitis were reviewed. These results were compared with the final diagnosis, based on the American College of Rheumatology 1990 criteria.

Results: FDG PET was ordered because of suspected vasculitis in 20 patients, because of fever of unknown origin in two patients, and for follow-up of vasculitis in five patients. Fourteen patients were diagnosed with vasculitis (giant cell arteritis n=5, polymyalgia rheumatica n=2, polyarteritis nodosa n=3, Takayasu n=1, Churge-Strauss n=1, Wegener's granulomatosis n=1, vasculitis skin n=1), two patients were diagnosed with fibromuscular dysplasia and one patient had media necrosis of the aorta. In five patients no diagnosis could be reached. FDG PET results were considered to be true-positive in ten patients, true-negative in 14 patients and false-negative in three patients resulting in a positive predictive value of 100% and a negative predictive value of 82%.

Conclusions: FDG PET appears to be a promising new imaging technique in diagnosing and determining the extent of various forms of vasculitis. Furthermore, FDG PET may become a useful tool for evaluating the effect of treatment of vasculitis.

INTRODUCTION

Early and accurate diagnosis and assessment of the extent of vasculitis is important for adequate therapeutic measures and improvement of prognosis. Diagnosing vasculitis is often difficult due to the absence of specific symptoms and signs, the limited specificity of the available biochemical tests and the limited sensitivity of detecting the frequently subtle vessel abnormalities with conventional imaging techniques. The various kinds of vasculitis are classified based on the type of inflammation, the predominant size of the involved arteries, and the extent and location of the inflammation. The American College of Rheumatology 1990 criteria for the classification of vasculitis (ACR criteria)[1-11] are considered to be the gold standard. Although these criteria were established for research, they are often used for clinical diagnosis of vasculitis. In a study of 198 patients suspected of vasculitis, however, the ACR criteria functioned poorly in the clinical diagnosis of specific types of vasculitis.[12] In clinical practice, diagnosing vasculitis and evaluating the extent and location of the disease is difficult or even impossible in many cases. In those types of vasculitis in which it is difficult to obtain histological proof, imaging techniques are used for diagnosis. Vasculitis of the medium-sized and large blood vessels can

[#] J.W.M. van der Meer was not involved in the handling and review process of this paper.

be detected by several radiological techniques including classic angiography, computerised tomography (CT), magnetic resonance imaging (MRI) and ultrasonography. Since these techniques only show anatomical changes of the vessel lumen, inflammation of the vessel wall cannot be detected in an early phase due to the lack of substantial anatomical changes at this time. Also, it is difficult if not impossible to distinguish active inflammatory lesions from residual anatomical changes due to previous inflammation.

Scintigraphic imaging is a noninvasive method allowing delineation of both localisation and number of foci in all parts of the body, based on functional changes of tissues. F-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) has become an established imaging tool in oncology and is now entering the field of infectious and inflammatory diseases.[13] FDG accumulates in organ tissues with a high rate of glycolysis,[14] which does not exclusively occur in neoplastic cells. Lesions with a high concentration of activated inflammatory cells also show increased uptake of FDG.[15,16] Furthermore, from almost all other sites of the body, including the blood compartment, it is cleared very rapidly. FDG PET could thus be a promising new imaging technique for evaluation of metabolic activity in the vessel wall in both diagnosis and follow-up of patients with vasculitis. FDG accumulation on PET scanning has been reported in patients with giant cell arteritis and polymyalgia rheumatica,[17-20] Takayasu's arteritis,[20-24] periaortitis due to Wegener's granulomatosis,[25] aortitis,[20,26] unspecified large vessel vasculitis[27,28] and infectious vasculitis.[29] To further assess the role of FDG PET imaging in diagnosis and follow-up of patients with different types of vasculitis, we evaluated the results of FDG PET scans, performed either because of suspected vasculitis or fever of unknown origin with results suggesting the presence of vasculitis.

MATERIALS AND METHODS

Patients

The results of all FDG PET scans ordered in the University Medical Centre of Nijmegen from January 1999 to April 2003 because of suspected vasculitis or fever of unknown origin with results suggesting the presence of vasculitis were reviewed. Fever of unknown origin was defined according to the revised Petersdorf criteria: a febrile illness of >3 weeks duration, a temperature of >38.3°C on several occasions, and no diagnosis after one week of evaluation in hospital or after three visits to the outpatient department.[30] The patients were evaluated with other imaging modalities and laboratory tests, as was considered clinically appropriate. Patients were included if the diagnostic process had been completed at the time of data analysis in April 2003. The patients with fever of unknown origin are also included in a retrospective study investigating the diagnostic contribution of FDG PET in patients with fever of unknown origin that will be published elsewhere.[31]

FDG PET

A dedicated, full-ring PET scanner (ECAT-EXACT, Siemens/CTI, Knoxville, Tenn., USA) was used for data acquisition. Prior to FDG injection patients had fasted for at least six hours. Intake of sugar-free liquids was permitted. Immediately prior to the procedure, the patients were hydrated with 500 ml of water. One hour after intravenous injection of 200 to 220 MBq FDG (Mallinckrodt Medical, Petten, the Netherlands) and 10 to 15 mg furosemide, emission images or emission and transmission images of the area between the proximal femora and the base of the skull were acquired (10 minutes per bed position). When only an emission study was recorded, the images were not corrected for attenuation and were reconstructed using filtered back protection (Butterworth filter with a cut-off frequency of 0.4 Nyquist). When emission and transmission studies were recorded, the images were corrected for attenuation and were reconstructed using the ordered subsets-expectation maximisation (OSEM) algorithm. Reconstructed images were displayed in coronal, transverse and sagittal planes.

Interpretation

FDG PET scans were interpreted by two staff members of the department of nuclear medicine blinded for other diagnostic test results and the final diagnosis. FDG PET scans were rated as normal or abnormal. Results were judged to be abnormal if focal accumulation of the tracer was detected outside of the areas of physiological uptake. Normally no visible FDG uptake is present in blood vessel walls. Disagreements were resolved by consensus.

Clinical assessment of test results and diagnosis

Results were considered to be true-positive when abnormal vascular FDG uptake was present in patients with a clinical diagnosis of vasculitis. Abnormal results were categorised as false-positive when the abnormality was not related to the illness or when no final diagnosis could be reached. A normal FDG PET scan was considered to be true-negative when no cause was identified for the symptoms despite an extensive diagnostic work-up. In cases of suspected vasculitis, the diagnostic work-up had to be complete according to the ACR criteria. A normal FDG PET scan was considered false-negative when vasculitis was diagnosed except for vasculitis limited to the brain because of known low sensitivity of FDG PET due to high physiological FDG uptake in the brain, or vasculitis limited to the legs, because the legs are not routinely imaged if not specially mentioned on the FDG PET request. A final diagnosis of

vasculitis was based on the ACR criteria. When this was not possible, a probable diagnosis was made based on clinical follow-up and conventional radiological studies. No criteria defining an exacerbation or recurrence of a known vasculitis syndrome are available. To define a probable exacerbation or recurrence, the clinical diagnosis based on a combination of recurrence of symptoms resembling the symptoms at the time of the first episode with vasculitis, an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) and other biochemical tests were used. The final or probable clinical diagnosis served as a standard of reference and was used for the comparisons with the FDG PET results.

RESULTS

From January 1999 to April 2003, 25 patients were referred for a total of 30 FDG PET scans because of suspected vasculitis or fever of unknown origin with FDG PET results indicating vasculitis. Three patients had to be excluded because of insufficient data in follow-up, so the results of 27 FDG PET scans in 22 patients were evaluated. Of these patients, two were male and 20 were female with a median age of 60 years (range 17 to 81 years). Nine patients had at least one period of hospitalisation with a median duration of 14 days (range 8 to 62 days). Thirteen patients only visited the outpatient department.

The clinical diagnoses of the patients are shown in *table 1*. Fourteen patients (64%) were diagnosed with vasculitis based on the ACR criteria. Fibromuscular dysplasia was diagnosed in two patients: one patient was diagnosed with fibromuscular dysplasia of the right renal artery and the hepatic artery based on typical changes on angiography, which is the gold standard for diagnosing this disease. In the other patient a probable diagnosis of fibromuscular dysplasia of the carotid arteries was reached based on typical changes on magnetic resonance angiography (MRA). One patient suspected of vasculitis of the thoracic aorta because of a progressively dilating ascending aorta and a variable elevation of CRP was eventually diagnosed with media necrosis of the ascending aorta after replacement of the affected part with an aortic graft. No signs of vasculitis or infection were found and the definite cause of the media necrosis remained unresolved. The media necrosis was possibly caused by previous aortitis in this patient with a combined immunodeficiency. In five patients suspected of vasculitis, no cause could be established for their symptoms after a median follow-up of seven months (range 1 to 17 months): one patient had persisting symptoms without treatment and died of cerebral haemorrhage 17 months after FDG PET (no autopsy was performed), two patients had persisting symptoms while treated with nonsteroidal anti-inflammatory drugs for one and six months, respectively, in one patient symptoms completely disappeared after prednisone treatment and in one patient severity of symptoms decreased and ESR normalised spontaneously.

Table 1
Clinical diagnosis in 22 patients suspected of vasculitis or with fever of unknown origin and FDG PET results indicating vasculitis

CATEGORY	NO. OF CASES
Vasculitis	14
Giant cell arteritis	5
Polymyalgia rheumatica	2
Polyarteritis nodosa	3
Takayasu	1
Churge-Strauss	1
Wegener's granulomatosis	1
Vasculitis skin (unspecified)	1
Fibromuscular dysplasia	2
Media necrosis aorta (of unknown origin)	1
No diagnosis	5

The median duration of symptoms before FDG PET was performed was five weeks (range 2 weeks to 41 months). In three patients (14%) the symptoms had persisted for more than six months before FDG PET was ordered. The first FDG PET scan was requested because of suspected vasculitis in 20 patients and because of fever of unknown origin in the remaining two patients. *Table 2* shows the classification of the FDG PET results. Ten of the total number of 22 'first' FDG PET scans were abnormal (45%) and all these abnormal FDG PET results were found in patients with active vasculitis and were thus considered to be true-positive. Examples are shown in *figures 1* and *2*. In two patients with active temporal arteritis and in one patient with vasculitis limited to the skin who had not been treated with corticosteroids, the results of FDG PET were classified as false-negative. Normal FDG PET results were categorised as true-negative in five patients in whom no diagnosis could be reached, in two patients with fibromuscular dysplasia, and in the patient with media necrosis. One patient with a history of Takayasu's arteritis, which had been inactive for almost four years, was suspected of recurrence of active vasculitis because of painful shoulders and a slightly elevated ESR. Symptoms spontaneously disappeared, ESR normalised and no diagnosis of recurrence of active vasculitis was made, so the normal FDG PET results were also considered to be true-negatives in this case.

In three patients with polyarteritis nodosa, one patient with temporal arteritis and one patient with Wegener's

Table 2
Classification of the results of 27 FDG PET scans in patients suspected of vasculitis or with fever of unknown origin with FDG PET results indicating vasculitis

CATEGORY	TRUE-POSITIVE	TRUE-NEGATIVE	FALSE-NEGATIVE	FALSE-POSITIVE
Vasculitis (diagnosis)	10	1	3	0
Vasculitis (follow-up)	0	5	0	0
Fibromuscular dysplasia	0	2	0	0
Media necrosis aorta	0	1	0	0
No diagnosis	0	5	0	0
Total	*10*	*14*	*3*	*0*

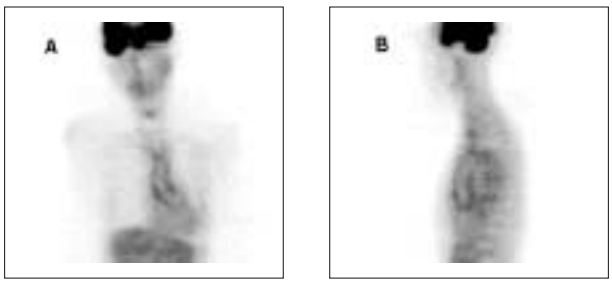

Figure 1
PET scan of an 80-year-old woman with temporal arteritis

This woman was diagnosed with temporal arteritis in 1999, based on the ACR criteria including typical changes on temporal artery biopsy. She responded well to high-dose prednisone, which was slowly tapered to 5 mg. She remained well until January 2002 when she presented with headaches, painful shoulders and weight loss (8 kg). Physical examination had not changed and revealed absence of pulsation of the temporal arteries, but was otherwise normal. ESR was slightly elevated to 22 mm/h (normal <12 mm/h). She did not respond to prednisone 20 mg daily. Since recurrence of giant cell arteritis was suspected, FDG PET was performed to evaluate whether her symptoms were caused by active vasculitis. PET demonstrated increased FDG uptake especially in the ascending aorta indicating active aortitis (A = coronal projection, B = sagittal projection). She was diagnosed with reactivation of giant cell arteritis and her symptoms disappeared again after high-dose prednisone treatment.

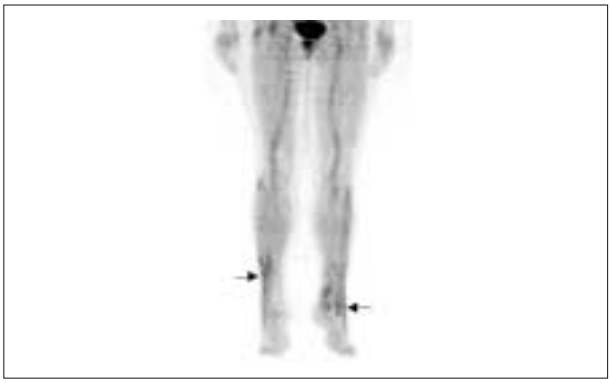

Figure 2
PET scan of a 60-year-old woman with myalgia of the lower legs, skin ulcerations on both legs, livedo reticularis and mild polyneuropathy

A skin biopsy of this previously healthy woman showed fibrosing panniculitis and necrotising vasculitis of medium-sized arteries. Polyarteritis nodosa was diagnosed according to the ACR criteria. FDG PET was performed to determine the extent of the vasculitis. Increased FDG uptake was found in both femoral arteries and several superficial lesions on the lower legs (arrows); the latter were probably caused by the skin ulcerations. No vascular FDG uptake was noticed elsewhere (not shown). She was treated with high-dose prednisone and her symptoms disappeared.

granulomatosis, a second FDG PET scan was performed to evaluate the effect of treatment with a median time between the first and second FDG PET scans of 11 weeks (range 4 to 25 weeks). FDG PET results were normal in these five patients who all had a good clinical and biochemical response to therapy (*table 2*). After the second FDG PET scan proved to be normal, the corticosteroid dose was tapered in all five patients without relapse of symptoms thus far. The results of these FDG PET scans were considered to be true-negative. The sensitivity of all 27 FDG PET scans in these 22 patients was 77%, specificity was 100%, positive predictive value was 100% and negative predictive value was 82%.

DISCUSSION

In this study we retrospectively evaluated the utility of FDG PET in diagnosis and follow-up of vasculitis. The results demonstrate that vascular FDG uptake is increased in different types of active vasculitis. To our knowledge, increased FDG uptake on PET scanning has not been reported before in patients with polyarteritis nodosa or Churge-Strauss syndrome. In addition, a remarkable decrease in FDG uptake corresponded well with improvement of symptoms and laboratory results in five patients, suggesting that vascular FDG uptake is only seen in active vasculitis and not in noninflammatory

vascular disease such as fibromuscular dysplasia or in inactive disease. Although inflammation of the arterial wall is most prominent in vasculitis, inflammation also contributes to atherogenesis. In an atherosclerotic rabbit model, increased FDG accumulation was shown in the affected arteries.[32] FDG uptake in the femoral and iliac arteries was increased in 133 patients with at least one risk factor for atherosclerosis when compared with 23 controls.[33] In our experience FDG uptake in vasculitis is much higher than in atherosclerosis, so a distinction between these two diagnoses may very well be possible.

Besides several case reports and a case series in patients with giant cell arteritis or polymyalgia rheumatica,[17,19,20] Takayasu's arteritis,[20-24] periaortitis due to Wegener's granulomatosis,[25] aortitis of the thoracic aorta[20,26] and large vessel vasculitis,[27,28] only two prospective studies exploring the diagnostic value of FDG PET imaging in vasculitis have been published. Blockmans *et al.*[18] found a sensitivity of FDG uptake in the large thoracic arteries for the diagnosis of temporal arteritis or polymyalgia rheumatica of 56%, a specificity of 98%, a positive predictive value of 93% and a negative predictive value of 80% in 25 patients with biopsy-proven temporal arteritis or polymyalgia rheumatica. The extent of the vasculitis to a much larger part of the arterial system than is usually suspected in giant cell arteritis was remarkable. It was also suggested that the results of this study support the hypothesis that polymyalgia rheumatica is caused by the same kind of vasculitis,[18] therefore these patients were included in the present study. Meller *et al.*[20] compared FDG PET with MRI in 15 patients with aortitis due to giant cell aortitis (n=14) or Takayasu's arteritis (n=1) at the time of diagnosis and during follow-up (n=7). It was concluded that FDG PET is a valuable technique in both diagnosis and follow-up of patients with aortitis, because it identified more vascular regions involved in the inflammatory process than did magnetic resonance imaging.[20] Sensitivity of FDG uptake in vasculitis in the study by Blockmans *et al.* seems to be lower when compared with the results of the present study (56 versus 77%). However, we found false-negative results in two out of seven patients diagnosed with temporal arteritis or polymyalgia rheumatica suggesting that sensitivity of FDG PET may be lower in these patients than in patients with other types of vasculitis. Due to high uptake in the brain, the small diameter of the vessel, and the relatively high background of the skin, direct evaluation of the temporal arteries is not possible on whole body PET imaging. This could explain the difficulty of detecting giant cell arteritis by FDG PET, especially in cases where vasculitis is really limited to the temporal arteries.

Conventional scintigraphic techniques have also been used occasionally in patients with vasculitis. In a prospective study of 19 patients with biopsy-proven temporal arteritis, gallium-67-citrate scintigraphy (Ga-67) had a 94% specificity and a 90% positive predictive value with normalisation of Ga-67 uptake after six months of steroid therapy.[34] In one study radio-labelled leucocyte scintigraphy seemed to be superior to conventional angiography and CT for detecting and monitoring vasculitic involvement of the respiratory tract.[35] In Takayasu's arteritis, however, indium-111-leucocyte scintigraphy had a low sensitivity for active disease.[36] Compared with conventional nuclear medicine techniques, advantages of FDG PET in diagnosing inflammation are early imaging (one hour), resulting in early reporting,[37] tomographic information with higher spatial resolution, resulting in more anatomic information, and high inter-observer agreement.[38]

Recently, imaging techniques for demonstrating anatomic blood vessel changes in vasculitis, such as CT angiography, MRI and colour duplex ultrasonography, have greatly improved. This improvement and the invasive nature of classic angiography makes one inclined to perform these imaging techniques instead of angiography in diagnosis and follow-up of patients with vasculitis. CT angiography is able to detect luminal and vessel wall changes in patients with Takayasu's arteritis with high accuracy.[39,40] Vascular wall thickening is also an important finding on MRI in the acute phase of Takayasu's arteritis, subsiding after appropriate therapy.[41,42] Mural oedema is a characteristic pattern of active and progressive Takayasu's arteritis, which is absent in the chronically active state.[43] In patients with giant cell arteritis, MRA is potentially useful for follow-up the effect of treatment.[44,45] Duplex ultrasonography is able to demonstrate luminal changes, aneurysms and a hypoechoic halo, most probably caused by vessel wall oedema, in patients with temporal arteritis and Takayasu's arteritis.[46-48] In a study of 86 patients with biopsy-proven temporal arteritis, it was concluded that colour duplex ultrasonography made only a modest contribution to diagnosing temporal arteritis.[49] In another study, duplex ultrasonography was found to be a noninvasive, relatively inexpensive, and efficient method, suitable for repeated follow-up in patients with Takayasu's arteritis.[40] However, ultrasonography is limited in the extent to which it can detect all diseased vessels, especially the pulmonary arteries, aorta and visceral vessels. Positive aspects of FDG PET imaging compared with CT, MRI and ultrasonography are whole-body screening, high contrast resolution, absence of disturbance by metallic implants (MRI) and absence of contrast-related side effects (CT). Also, FDG PET shows functional changes caused by activation of inflammatory cells and does not depend on anatomical changes in contrast to CT, MRI and ultrasonography. Disadvantages of FDG PET are the higher cost, still limited availability and more limited anatomic information due to lower spatial resolution as compared with CT and MRI.

In conclusion, FDG PET appears to be a valuable new imaging technique in diagnosing and determining the extent of various forms of vasculitis. Furthermore, FDG PET may become a useful tool for evaluating the effect of treatment of vasculitis that cannot reliably be visualised by conventional techniques. However, for a validation of FDG PET in patients with suspected vasculitis and for determination of its exact position in the follow-up of response to treatment, prospective studies in a larger number of patients are warranted.

NOTE

Data from this manuscript were presented at the Annual Congress of the European Association of Nuclear Medicine in Amsterdam, the Netherlands from 23 to 27 August 2003.

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