ABSTRACT

Objectives. To determine the value of Positron Emission Tomography (PET) in the diagnosis of Takayasu arteritis (TA) and giant cell arteritis (GCA) and its value in the assessment of disease activity and response to therapy.

Methods. In 5 consecutive patients diagnosed with TA or GCA, PET using the tracer F18-deoxyglucose (FDG) was performed when disease activity was suspected based on clinical and laboratory parameters. PET was repeated after therapeutic intervention when disease remission was achieved. PET findings were compared with angiography, MRA and clinical parameters.

Results. PET visualised inflamed arteries in all 5 patients, but there was a discrepancy between PET and angiography or MRA. In 8 arteries of 4 patients only PET showed disease involvement, while in 5 arteries of 2 patients only angiography or MRA showed involvement. After treatment and the disappearance of clinical symptoms, FDG uptake was clearly reduced compared to the initial scan in all patients. In all but one the acute phase response declined. In that patient a urinary tract infection explained the elevated acute phase response, as this normalised after antibiotic treatment.

Conclusion. PET is a promising new technique for the diagnosis of large vessel vasculitides. Furthermore, PET appears to be a valuable tool for the assessment of disease activity during follow-up and of the response to therapy.

Introduction

The vasculitides are a heterogeneous group of syndromes characterised by inflammation of blood vessels. The clinical features depend on the size and distribution of the involved vessels. Giant cell arteritis (GCA) and Takayasu arteritis (TA) are examples of vasculitides of the large vessels. GCA predominantly affects the supra-aortic arteries, especially the superficial temporal artery, although the aorta and its main branches may also be involved (1-3). TA primarily affects large arteries, in particular the aorta and its branches such as the subclavian arteries (4, 5).

Preferentially, diagnosis in GCA and TA is made by biopsy. However, biopsies of large vessels are difficult to obtain and may yield false negative results. In one study, about 15% of patients who met the ACR criteria for GCA had a negative temporal biopsy (6). Therefore, non-invasive methods such as duplex sonography and magnetic resonance angiography (MRA) have been investigated. However, the sensitivity of duplex sonography is rather low (50%) (7, 8), while experience with and the availability of MRA is still limited (9-11). Therefore, other non-invasive methods which visualise inflammation of the large arteries are still required.

The course of GCA (especially when large arteries are involved) and of TA is rather variable. These syndromes usually extend for many years and are characterised by varying degrees of activity. Active disease is characterised by vascular inflammation that may result in irreversible structural abnormalities. Therefore, it is important to detect disease activity at presentation of the disease and during follow-up as early as possible, to allow treatment when vessel wall changes are still reversible and to prevent further damage. However, no sensitive and specific markers of disease activity are available. For example, measurement of acute phase reactants is relatively insensitive and identifies only 50% of all patients with active disease (12-14). Positron Emission Tomography (PET) might offer new possibilities to over-
come the problems of diagnosis and adequate follow-up. PET using the tracer F18-deoxyglucose (FDG) is a non-invasive imaging technique with clinical applications in oncology. Up-
take of FDG is based on increased glu-
cose metabolism, as is nearly always present in malignant cells. In active in-
flammatory cells such as macrophages, avid uptake is also found (15,16). For oncological purposes this uptake may interfere with tumor assessment, but in inflammatory diseases the technique might be used to visualise active inflammation. The method could be ben-
eficial in diagnosing the disease and in treatment evaluation. Several reports support the use of FDG PET in the diagnosis of inflammatory diseases such as GCA (17-19), polymyalgia rheumatica (17) and TA(20,21). Others have examined the value of FDG PET in patients with FUO (22,23). In this report we evaluated whether: (i) FDG PET could identify sites of inflamma-
tion in patients with large vessel vasculitides during active disease; (ii) artery involvement detected by FDG PET was in accordance with the affect-
ed arteries found by other imaging pro-
cedures; and (iii) FDG PET could be used in the follow-up of these patients.

Patients and methods
Five consecutive patients who fulfilled the modified American College of Rheumatology diagnostic criteria for TA (n = 3) or GCA (n = 2) were includ-
ed in this study (Table I) (24, 25).
In all patients a FDG PET scan was performed at least twice. The first PET
scan was acquired when an active stage
of the disease was suspected based on the criteria described in Table II (13, 26). After confirmation of active dis-
ease, therapy was intensified. In all pa-
tients the PET scan was repeated when evidence of disease activity had disap-
peared. The average interval between the scans was 10 months (range 2 months to 24 months).
Whole body 2D-PET images were ac-
quired 90 min after the administration
of 400 MBq FDG, on a Siemens ECAT
951/31 or HR+ positron camera with-
out attenuation correction (7/10 scans).
Images were reconstructed using itera-
tive algorithms. Without knowledge of the clinical or radiological data, images were analysed by a blinded and experi-
enced PET nuclear medicine specialist.

### Table I. Basic characteristics of the patients.

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Sex</th>
<th>Age</th>
<th>GCA/ TA</th>
<th>Age at TA onset</th>
<th>Methods of diagnosis</th>
<th>Artery involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>19</td>
<td>TA</td>
<td>19</td>
<td>CT-angiography, duplex ultrasonography</td>
<td>Common carotid artery R/L</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>32</td>
<td>TA</td>
<td>30</td>
<td>MRA</td>
<td>Common carotid artery R/L</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>36</td>
<td>TA</td>
<td>27</td>
<td>Angiography, Abdominal aorta</td>
<td>Aortic arch</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>67</td>
<td>GCA</td>
<td>65</td>
<td>Angiography, duplex ultrasonography, Internal carotid artery L, Brachial artery R</td>
<td>Common carotid artery L, Subclavian artery R/L</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>80</td>
<td>GCA</td>
<td>79</td>
<td>Angiography, duplex ultrasonography</td>
<td>Subclavian artery R/L</td>
</tr>
</tbody>
</table>

CT: computed tomography; MRA: magnetic resonance angiography.

### Table II. Criteria for active GCA and TA(refs. 10, 22).

<table>
<thead>
<tr>
<th>GCA</th>
<th>TA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flare in disease activity by the presence of one of the following criteria</td>
<td>Active disease (new/worsening of 2 or more features)</td>
</tr>
<tr>
<td>- New headache</td>
<td>- Systemic features, such as fever and arthralgia</td>
</tr>
<tr>
<td>- Scalp/arterial tenderness</td>
<td>- Elevated acute phase proteins</td>
</tr>
<tr>
<td>- New jaw claudication</td>
<td>- Features of vascular ischemia or inflammation</td>
</tr>
<tr>
<td>- Fever in the absence of infection</td>
<td>- Typical imaging features</td>
</tr>
<tr>
<td>- New visual deficit</td>
<td>- New arterial bruits (cervical, supraclavicular, or brachial)</td>
</tr>
<tr>
<td>- Symptoms of polymyalgia rheumatica</td>
<td>- Increase in global disease activity as assessed by the physician</td>
</tr>
</tbody>
</table>

### Results

**Case descriptions**
Patient 1. A 19-year-old woman com-
plained of fatigue, weight loss and lost appetite for 18 months. On clinical in-
vestigation a bruit over the right carotid artery and a decreased artery pulse in her feet were found. The CRPlevel was elevated (124 mg/l). Duplex scanning demonstrated thickening of the wall of the common carotid artery. Computed Tomography (CT) angiography of the abdomen revealed edema in the wall of the abdominal aorta. Based on these findings TA was diagnosed. PET scint-
tigraphy showed remarkable uptake in the aortic arch, the carotid artery, the pulmonary artery and the abdominal aorta (Fig.1). Therapy with prednis-
one (60 mg once daily) was initiated.
After 2 months her complaints disappeared and the CRP level normalised. The repeat PET scan showed no abnormalities.

Patient 2. A 30-year-old female presented with fatigue, exertional dyspnoea and non-specific pain in her chest. Clinical investigation revealed a bruit over the left carotid artery. The CRP level was elevated (36 mg/l). MRA visualised irregular vessel walls in the right and left common carotid arteries. The PET scan showed only elevated uptake in the left subclavian artery. Treatment with prednisolone at 60 mg once daily was started. The patient responded very well. The symptoms disappeared and the CRP level normalised. The FDG-uptake on the repeated PET scan had considerably diminished as compared with the first scan.

Patient 3. A 36-year-old female had an established TA, diagnosed by conventional angiography, for 9 years. Despite treatment with 10 mg prednisolone and 150 mg azathioprine once daily, the patient remained fatigued and suffered from malaise. The CRP level remained elevated (21 mg/l). There was doubt about disease activity. To differentiate between disease activity and other causes of less well being and an elevated CRP level, a PET scan was performed, which showed modest uptake in the aortic arch and abdominal aorta. Prednisolone was raised to 30 mg once daily and cyclosporine (250 mg) was added. However, after 6 months the patient still complained about fatigue. CRP was still elevated (28 mg/l). Repeated PET scan showed unaltered FDG uptake in the abdominal aorta. Azathioprine and cyclosporine were stopped and mycophenolate mofetil (3 g) was started. Gradually the patient felt less fatigue and the CRP level declined (13 mg/l). The repeated PET scan performed 16 months after the second scan, showed less FDG uptake compared to the previous ones.

Patient 4. A 65-year-old female suffered from headache for more than 18 months. Next to headache she complained about malaise existing for 3 months. During clinical investigation her blood pressure was undetectable and the artery pulse was remarkably decreased in both arms. The CRP level was elevated to 106 mg/l. MRA visualised irregular vessel walls in the right and left common carotid arteries. The PET scan showed only elevated uptake in the left subclavian artery. Treatment with prednisolone at 60 mg once daily was started. The patient responded very well. The symptoms disappeared and the CRP level normalised. However, at the moment the second PET scan was performed, the CRP level had risen again to 17 mg/l. Although almost all uptake had disappeared on this repeat scan, some uptake was still seen in the aortic arch (Fig. 2).

Patient 5. A 79-year-old female com-

<table>
<thead>
<tr>
<th>Pt.</th>
<th>First PET findings</th>
<th>CRP (mg/l)</th>
<th>Second PET findings</th>
<th>CRP (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Aortic arch</td>
<td>+++</td>
<td>Aortic arch</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Carotid artery R/L</td>
<td>+++</td>
<td>Carotid artery R/L</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Pulmonary artery</td>
<td>+++</td>
<td>Pulmonary artery</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Aorta abdominal</td>
<td>++</td>
<td>Aorta abdominal</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Subclavian artery L</td>
<td>++</td>
<td>Subclavian artery L</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Popliteal artery</td>
<td>-</td>
<td>Popliteal artery</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>Aortic arch</td>
<td>+++</td>
<td>Aortic arch</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Descending aorta</td>
<td>+</td>
<td>Descending aorta</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>Aortic arch</td>
<td>+++</td>
<td>Aortic arch</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>Subclavian artery R/L</td>
<td>++</td>
<td>Subclavian artery R/L</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Aorta abdominal</td>
<td>++</td>
<td>Aorta abdominal</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Subclavian artery R/L</td>
<td>++</td>
<td>Subclavian artery R/L</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Carotid origin</td>
<td>++</td>
<td>Carotid origin</td>
<td>+</td>
</tr>
</tbody>
</table>
plained about myalgia existing one year. In the last 3 months she also suffered from fatigue and loss of appetite. GCA was suspected based on the Doppler sonography findings. The diagnosis was confirmed by conventional angiography, as it showed stenosis and post-stenotic dilatation in both subclavian arteries. Before treatment with prednisolone (60 mg daily) was started, a first PET scan was performed. Elevated FDG uptake was seen in both subclavian arteries and the carotid origin. Initially the response to therapy was good. Symptoms were no longer present and the CRP level normalised (from 50 mg/l to <3 mg/l). However, after 6 months the CRP level rose again (50 mg/l), although the patient was without complaints. To differentiate between disease activity and another cause of the increased CRP level, the patient underwent a second PET scan that no longer showed elevated FDG uptake. Treatment was not intensified and further evaluation showed a urine tract infection, confirmed by a culture. After antibiotic treatment the CRP level decreased to 4 mg/l.

Comparison of angiographic and PET findings

To study the potential role of PET in diagnosing large vessel vasculitides, the number of arteries showing elevated FDG uptake as demonstrated by PET were compared with the number seen by angiography or MRA (Tables I and II). Based on angiography, considered as the gold standard to evaluate the vessel lumen, there was involvement at 13 sites in the major arteries. PET detected 8 of these (62%): the right and left common carotid arteries and abdominal aorta in patient 1; the aortic arch and the abdominal aorta in patient 3; the left subclavian artery in patient 4; and the right and left subclavian arteries in patient 5.

However, some discrepancies were also found. PET showed clear uptake in 8 vessels in which no anatomical abnormalities were found on angiography. Those arteries were the aortic arch and the pulmonary artery in patient 1; the popliteal artery and the left subclavian artery in patient 2, the aortic arch, the abdominal aorta and the right subclavian artery in patient 4, and the carotid origin in patient 5. Five arteries were normal on the PET scan – the right and left common carotid arteries in patient 2 and the left internal and common carotid arteries and the right brachial artery in patient 4. In contrast, angiography or MRA demonstrated vascular luminal changes in those 5 arteries.

Comparison of PET findings obtained during active and clinically quiescent disease

Finally, we analysed whether PET could be a valuable tool for the assessment of disease activity, in conjunction with the clinical symptoms and the CRP level. FDG uptake during active disease was compared with uptake when disease remission was judged to have been achieved based on clinical findings. FDG uptake decreased after therapeutic intervention in all patients, confirming the response to therapy (Table II). In patient 1 the PET scan normalised completely, whereas in the other patients the second PET scan still showed minor uptake of the involved arteries.

Discussion

This study describes 5 patients in whom FDG PET was performed after diagnosing large vessel vasculitis and shows that PET seems to be a promising tool to diagnose GCA and TA and to monitor disease activity. Our results furthermore indicate that PET and angiography or MRA might complement each other, as some discrepancies between the methods were found. PET visualises active inflammation, while angiography and MRA show anatomical lesions, in particular stenosis and occlusions. Therefore, PET may show inflammatory changes while the angiography is still normal. On the other hand, after progression to the late phase of the disease with stenosis and occlusions, inflammation may have disappeared and PET might not show the irreversible anatomical changes seen on angiography or MRA.

It could be argued that the increased FDG uptake in the aortic arch might not be specific for large vessel vasculitis. Also in active atherosclerosis the aortic arch may become visible, presumably based on FDG uptake in metabolically active parts of atherosclerotic plaques, which is also a type of inflammatory reaction (27). In general, FDG uptake cannot be regarded as specific for inflammation, as other types of vessel damage and subsequent ‘repair’ may be associated with increased FDG uptake. However, although the nature of this FDG uptake cannot be derived from the images and histological evidence is impossible to obtain, atherosclerosis typically presents in older patients. In addition, increased atherosclerotic uptake in other vessels such as the carotid, popliteal or subclavian arteries, is rather uncommon on PET scans in daily practice.
To examine the value of PET in monitoring disease activity, a PET scan was performed during active and clinically quiescent disease. After therapeutic intervention, FDG uptake on PET scan decreased in all patients, but in 4 patients the last scan showed still some minor uptake. It is possible that the scan was performed when minor disease activity was still present while the clinical manifestations had already disappeared. At present, it is unknown whether the absence of clinical signs of disease activity, together with a decrease or even normalisation of the acute phase response, truly affects disease remission. Our findings suggest that ongoing (subclinical) disease activity still might be present in (a subset of) patients with large vessel vasculitis, supporting the use of PET to detect this ongoing disease activity. Furthermore, as demonstrated by patient 5, PET could be used to discriminate between disease activity and other causes of an elevated CRP level. Therefore, PET could be a safe, non-invasive diagnostic tool to aid clinicians in making decisions about providing therapy (28).

Apart from PET imaging, several other imaging techniques have been applied for the diagnosis and follow-up of GCA and TA. Computed Tomography (CT) scanning visualises pathologic changes of the large deep vessels, like dissections, ruptures, thrombus formation and calcifications. In large vessel vasculitides this technique can be used for evaluation of the wall changes in the aorta and pulmonary artery (29, 30). The application of CT in follow-up studies is limited, because of its still high radiation dose and the need for iodinated contrast medium. Also, the spatial resolution of 1-2 mm may not be enough to assess medium sized arteries (31).

Another quick, non-invasive technique to detect the characteristic wall thickening of arteries in large vessel vasculitis is sonography (8, 32-34). Colour Doppler sonography has been described as a successful non-invasive method to detect early TA and to monitor disease progression and response to therapy (35). Also in the present study sonography showed abnormal findings in TA patients. Sonography is, however, time consuming, operator-dependent, and technically difficult for assessing the subclavian arteries, which are the vessels most commonly involved in TA.

Magnetic resonance imaging (MRI) can be used to diagnose an early stage of large vessel vasculitis by assessing changes in vascular anatomy, mainly by evaluating aortic wall thickening. Also in the follow-up of patients with large vessel vasculitis, MRI can be applied. However, current data suggest that this technique is less suitable to evaluate disease activity and the response to therapy in GCA and TA, because no consistent correlation was found between MRI findings and clinical and laboratory parameters of disease activity (9, 20, 36). MRA represents the most recent improvement in MRI technique for vascular purposes. Through the use of gadolinium, a paramagnetic agent, the T1 relaxation time is shortened, which makes the blood brighter on T1-weighted images. This technique clearly depicts aortic lesions, including stenosis and dilatation, and is very suitable as a diagnostic tool for patients suspected to have large vessel vasculitis. Yamada et al. even estimated the sensitivity, specificity and accuracy of MRA for the diagnosis of TA to be 100% (10). Furthermore, in contrast to MRI, MRA was helpful in the assessment of disease activity and could be used in the follow-up of patients with large vessel vasculitis (9, 11). However, in the patient who underwent both MRA and PET, we showed that the techniques do not seem to be equivalent in detecting active inflammation in TA. Compared with the other techniques, PET seems to be valuable in diagnosing large vessel vasculitis in an early phase and in the assessment of disease activity. In addition, PET imaging involves the whole body, has a high contrast resolution and contrast-related side effects are absent. Nevertheless, some disadvantages – such as higher costs, limited availability and more limited anatomic information due to its lower spatial resolution as compared with CT and MRI – must be acknowledged (37).

Our findings concerning the use of non-invasive PET scan in diagnosing large vessel vasculitis confirm the results of others (17, 19-23, 38-40), including a recent study of Meller et al. (21).

In that study PET and MRI were compared in 5 patients with early TA. PET revealed a suitable whole body screening method in the primary diagnosis of early TA, especially in those cases that present with uncharacteristic symptoms such as FUO. Unfortunately, the value of PET in the follow-up of patients with TA was not evaluated. The possible value of PET in the follow-up of patients with TA has only been described in one case report (38). In that paper, FDG uptake normalised after high dose corticosteroid therapy, which is entirely in accordance with the results we present for our TA patients. The value of PET in the follow-up of patients with GCAs is supported by another study of Meller et al. (20). PET was performed initially and during the follow-up of 6 patients with GCA. After therapy with corticosteroids, 80% of the regions with initial pathological uptake showed normalisation, correlating with the clinical improvement and normalisation of laboratory findings seen. Two other case reports also demonstrated a decrease in FDG uptake in GCA patients after treatment (19, 41).

In conclusion, this report demonstrates that FDG PET not only seems to be a valuable additional tool for the diagnosis of large vessel vasculitis, but also may be helpful in the evaluation of disease activity and in the assessment of the response to therapy.

References
PET in large vessel vasculitides / K. de Leeuw et al.


