[18F] FDG-PET/CT as a new and sensitive imaging method for the diagnosis of large vessel vasculitis

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ABSTRACT

Objective. *To determine the value of the new imaging modality positron-emission tomography/computed tomography (PET/CT) for the diagnosis and re-evaluation of large vessel vasculitis.*

Methods. *Thirteen patients newly diagnosed or re-evaluated for suspected clinical disease activity of Takayasu arteritis (TA, 3 patients) or giant cell arteritis (GCA, 10 patients) underwent PET/CT. Clinical activity status, serological markers, and alternative imaging methods were evaluated.*

Results. *In patients with clinical activity despite nearly normal erythrocyte sedimentation rate (ESR) and C reactive protein (CRP), disease activity could be shown by PET-CT. A long segmental, increased fluoro-deoxyglucose (FDG) uptake in the vessel wall served as confirmation of the vascular inflammation. The aortic arch was involved in all patients with active disease (n=12). In the complementary CT scans, stenotic lesions were found in 8 out of 13 patients. Duplex ultrasonography was performed in 11/13 patients and was positive in nine of these patients at least at one site. Magnetic resonance imaging (MRI) was done for confirmation in 10 patients.*

Conclusion. *Doppler ultrasonography is a very useful and widely available method to confirm a first suspicion of vasculitis, but it has limitations especially at the large thoracic vessels, which are affected in many cases. ESR and CRP alone are not sufficient to evaluate disease activity. The new imaging modality PET/CT provides the additional information. It allows the evaluation of disease activity and vessel morphology as well as the localization of the inflammatory process in the same session.*

Competing interests: none declared.

Introduction

Takayasu (TA) and giant cell arteritis (GCA) both are large vessel vasculitides. Involvement of the aorta and its major branches is common in GCA, not only in TA. This has been underestimated before newer imaging tools such as magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) and PET have become available (1, 2). TA primarily affects the aorta and its major branches. It is more common among Asian patients but is seen in all races and mainly affects young (<40 years) females (1, 3). In GCA vessel inflammation most commonly involves the supra-aortic, cranial branches, especially the temporal artery. Patients are usually older than 50 years and the most common symptoms are headache, fever, jaw claudication, visual loss and polymyalgia (2, 4, 5). Both are progressive diseases, leading – after an early inflammatory phase – to stenosis or aneurysm formation, resulting in limb or organ ischemia (2, 3, 6). Standard treatment for both diseases are glucocorticosteroids (GC). Immunosuppressive agents such as methotrexate, azathioprine or cyclophosphamide may be effective but have been discussed controversially (2, 7-10).

There are classification criteria of the American College of Rheumatology (ACR) for both diseases (4, 11). Specific serological markers are not available and histopathology for diagnosis can only be arranged in GCA – with concomitant temporal arteritis – by biopsy of the temporal artery or after revascularization procedures in TA (3, 5). Disease activity can be estimated from the levels of inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

[18F] fluoro-deoxyglucose positron emission tomography (FDG-PET) is used to detect hypermetabolic areas such as malignant tumours or inflammatory lesions. CT provides the anatomical information, *e.g.*, the localization of the inflammation or the luminal

changes due to the vasculitis. Since 1999 several studies described the value of FDG-PET in the diagnosis of vasculitis of larger vessels (12-17). Positron emission tomography/computed tomography (PET/CT) is a new imaging tool, which allows a more precise localization of pathologic changes in PET by adding a high-quality CT scan in the same session. Kobayashi *et al*. (12) were the first to examine the use of a fusion of PET and CT images in TA. We report on 13 patients, 3 with Takayasu and 10 with Giant Cell arteritis who were newly diagnosed or reevaluated because of clinical and/or serological disease activity. The aim of this study was to explore the benefit of PET/CT as a diagnostic tool and for evaluation of inflammatory activity and its distribution.

Materials and methods

PET/CT scan

PET/CT investigations were performed using a whole-body PET/CT scanner (Biograph 16, Siemens, Erlangen, Germany) with lutetium oxyorthosilicate (LSO) detector (PET) and 16-slice multi-slice-CT (MSCT). [^{18}F] FDG was injected after patient informed consent and overnight fast for at least 12 hours. Blood glucose levels were lower than 120 mg/dl in all patients. Image acquisition started one hour after intravenous administration of 426 MBq (390-488 MBq) [^{18}F] FDG. MSCT with intravenous and oral contrast media were performed immediately prior to the [^{18}F]-FDG-PET scan. PET scans were processed using iterative reconstruction; the CT scans were used for attenuation correction. The co-registered images were subsequently fused and reconstructed in transaxial, sagittal and coronal planes. A region of interest (ROI) was manually placed on the vascular wall in the transaxial image surrounding the most intense area of ^{18}F-FDG uptake. The scans were interpreted independently by at least 2 experts in nuclear medicine and radiology. FDG uptake was evaluated visually and calculated as standardized uptake values (SUVs) according to the formula SUV=activity concentration/(injected dose/body weight). Our results refer to the maximum SUV measured of 6 defined locations: the ascending aorta, the descending thoracic aorta, the abdominal aorta, the supraaortic branches (subclavian, common carotid and axillary arteries), the iliac arteries and the femoral arteries, always focusing on the

Table I. Demographic data, clinical symptoms, serological markers and SUVs of the vasculitis patients and the control group are shown. In addition, the treatment at the time of PET/CT and the alternative imaging method which confirmed the diagnosis is mentioned where available.

Patient	Sex	Age years	Diag	DD Month	Symptoms	ESR mm/h (0-20)	BVAS new	CRP mg/dl (0-0.5)	Max SUV	Therapy at time of PET/CT	Alternative imaging method
1	F	45	TA	4	pulselessness, arm claudication, bruits sc	61	7	6.12	5.8	no	MRI whole body, US
2	F	50	TA	3	abdominal pain, weight loss, bruit aorta	22	7	0.32	2.7	Pred 7.5mg, AZA	-
3	F	41	TA	7	abdominal pain postprandial, diarrhoea, bruit aorta	88	13	8.15	2.5	no	MRI Aorta, US
4	F	65	GCA	14	headache, jaw claudication	6	6	1.05	5.2	Pred 7.5mg, CYC 750mg/m^2	US
5	F	63	GCA	10	abdominal pain, diarrhoea, cutaneous ulcers	9	20	1.77	2.5	Pred 10mg, MTX 15mg	MRA Aorta, US
6	F	65	GCA	17	pulselessness, arm claudication	23	6	1.27	4.0	no	MRI Aorta, US
7	M	61	GCA	4	pulselessness, myalgia, leg claudication	94	6	8.55	6.8	no	MRI Aorta, US
8	F	59	GCA	5	pulselessness, arm claudication	56	6	1.45	3.7	no	MRI Aorta, US
9	F	72	GCA	12	pulselessness, arm claudication	42	11	0.51	3.6	Pred 20mg	MRA Aorta, US
10	F	62	GCA	4	Myalgia, weight loss, anaemia	102	5	9.68	3.2	no	MRI Aorta US
11	F	71	GCA	6	pulselessness, myalgia, cutaneous ulcers	69	6	1.43	1.9	Pred 5mg	US
12	M	62	GCA	2	cutaneous ulcers, fever, weight loss	75	13	8.7	4.2	Pred 50mg	MRI Aorta
13	F	66	GCA	1	headache, myalgia, visual loss	19	9	0.16	-	Pred 20mg	MRI Aorta, US
Control	W	49	-		-	-	-	-	2.3	-	-
Control	W	66	-		-	-	-	-	1.4	-	-
Control	M	62	-		-	-	-	-	2.3	-	-
Control	W	47	-		-	-	-	-	1.8	-	-
Control	W	63	-		-	-	-	-	2	-	-
Control	W	72	-		-	-	-	-	1.8	-	-
Control	W	38	-		-	-	-	-	1.8	-	-
Control	M	61	-		-	-	-	-	2	-	-

TA: Takayasu arteritis; GCA: giant cell arteritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SUV: standardized uptake values; BVAS: Birmingham vasculitis activity score; postprand: postprandial; DD: disease duration; Diag: diagnosis; Pred: prednisolone; AZA: azathioprine; MTX: methotrexate; CYC: cyclophosphamide; SC: subclavian artery; US: Doppler Ultrasonography; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography.

region which visually had the highest accumulation.

Patients

Between January 2005 and November 2006 13 consecutive patients with large vessel vasculitis were newly diagnosed or re-evaluated. Discrimination between the two entities sometimes is difficult and we used the age (cut-off > 50 years) to estimate the diagnosis. Eight patients already received treatment for their vasculitis when PET/CT was performed (Table I). Only patients with suspected clinical disease activity were included. The clinical status of disease activity was assessed by an experienced rheumatologist by using the Birmingham Vasculitis Activity Score (BVAS) (17). ESR (normal value 0-20mm/h) and CRP (0-0.5mg/dl) as serological markers for inflammation at the time of PET/CT were estimated.

In 11 of the 13 patients, colour duplex ultrasonography (US) of the temporal artery, the carotids and the vertebral and subclavian arteries was performed in addition to PET/CT scan, and in 10/13 patients a second imaging modality at the same time was applied (mean interval between PET-CT and second modality: 10 days) with unchanged treatment and clinical activity (MRI aorta, whole body MRI or MRA). To confirm the diagnosis of vasculitis by duplex ultrasound, patients had to show either a typical "halo sign" with or without stenosis (19, 20) or contrast enhancement and wall thickening with or without stenosis in the MRI (13, 21, 22).

Eight patients with solid malignant tumours who underwent PET/CT for restaging after successful resection of the tumour served as controls. Patients with tumour activity and lymphomas were excluded.

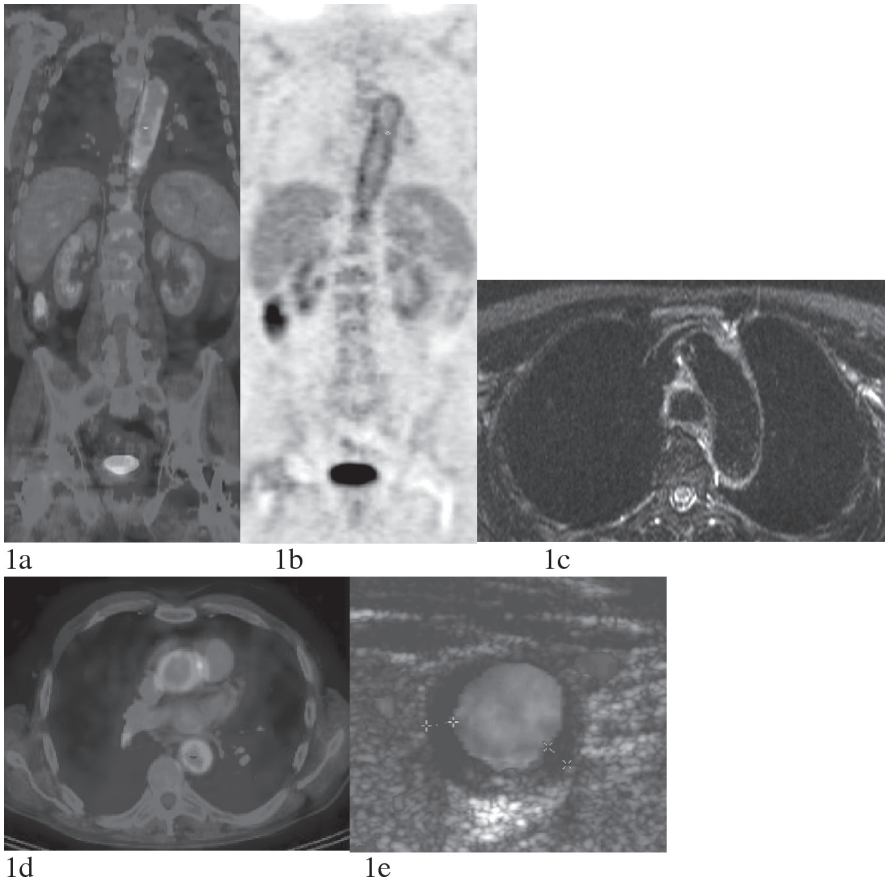

Fig. 1. Patient no. 7 showing high FDG uptake in the coronal reconstructions in the fused images (**1a**) and only PET (**1b**) with circular enhancement in the transversal scans (**1d**). The MRI reveals the vasculitis with contrast enhancement of the aortic wall (**1c**). 1e shows the typical halo in the duplex ultrasound of the subclavian artery. An additional coloscopy could rule out pathology in the right colon despite FDG uptake (**1a/b**).

Results

Ten patients were diagnosed with GCA and 3 patients with TA. The median age of the patients was 62 years (41-72) at the time of diagnosis (Takayasu: 45 years, GCA: 63 years). The male to female ratio was 2:11. All patients were European Caucasians (11 German, 1 Serbian, 1 Greek). Disease duration – defined as the time of the first symptoms to the PET/CT examination – was 6.8 months (range 1-17 months). The most common symptoms were arm and leg claudication with pulselessness, abdominal pain (especially postprandial) and general symptoms such as fatigue, fever or myalgia/arthralgia. Only 2 patients had a temporal artery biopsy (patient 4+6), both showing typical histology for giant cell arteritis. The demographic data and symptoms of our patients are shown in Table I as are the serological markers and the maximum SUVs.

The mean ESR was 51 mm/h, the mean CRP 3,8 mg/dl. Those patients who were newly diagnosed and did not receive treatment at the time of the PET/CT (n=6) had a mean ESR of 71mm/h and the mean CRP was 5,9 mg/dl in contrast to a mean ESR of 34 mm/h and a mean CRP of 2 mg/dl in those patients who already received treatment. The mean SUV_{max} of all patients was 3.4 (3.9 without treatment versus 3.0 with treatment) measured over those arteries showing increased FDG uptake.

Tables II and III depict the affected arteries as seen in the PET/CT scan and the corresponding SUVs. 12/13 patients showed a pathologically increased FDG uptake over a longer segment of the arterial wall in the sagital and coronal images. In the axial scans this appears as a circular enhancement (Fig. 1). 12 patients had increased FDG uptake in the ascending aorta, 11/12 in the descending and 9/12 in the abdominal aorta. Especially the giant cell arteritis patients (patients 4-13) had an involvement of the supraaortic branches (9/10). Five patients showed an increased FDG uptake in all examined arteries, but not all of them had highly elevated acute phase reactants. The maximum SUV of all patients ranged from 1.6 to 6.8. Patient 13 had been diagnosed as giant cell arteritis with visual loss, elevated

Table II. Duplex ultrasound in comparison to PET/CT and MRI: Only 1 patient had a positive PET/CT and a negative ultrasound examination. Duplex ultrasound was done only for the supraaortic arteries (subclavian, carotids, axillary, vertebral arteries) in most patients, this explains why the stenosis of the celiac trunk could not be seen in patient 3. Wall thickening/contrast enhancement could not be evaluated in the MR angiography.

Patient	Ultrasound Halo/localization	Ultrasound: Stenosis seen/localization	PET: Typical FDG uptake localization	CT: Stenosis seen/localization	MRI: Contrast enhancement Method/localization	MRI: Stenosis localization
1	pos/sc, ax, car	yes: car, sc	Asc ao, desc ao, sc, car	yes: sc	Whole body: ver, sc	ver, sc
2	nd	nd	Asc ao, aa, ia	nd	nd	Nd
3	neg/ -	no	Asc ao, desc ao, aa, ia	yes: tru co	MRI aorta: aa, tru co	Tru co
4	pos/ ax, car	yes: sc	Asc ao, desc ao, aa, sc, ia, fem	yes: sc	nd	Nd
5	pos/car	yes: tru co, mes, ren	Asc ao, desc ao, sc	yes: tru co, mes, ren, fem	MRA aorta: -	Aa, ren, ai, fem
6	pos/sc, ax, car, ver	yes: ax, car	Asc ao, desc ao, aa, sc, car, ia, fem	yes: ax, car, ver	MRI aorta: asc ao, desc ao, sc, car, ver	Sc, car, vert
7	pos/sc, ax	yes: ax	Asc ao, desc ao, aa, car, ia, fem	yes: ax	MRI aorta: asc aorta, car	No
8	pos/sc, ax	yes: sc, ax	Asc ao, desc ao, sc, ia	yes: sc, ax	MRA aorta: -	Sc, ax
9	pos/sc, car	no	Asc ao, desc, ao, sc	no	MRI aorta: sc, asc ao	Sc
10	pos/car, sc, ax	no	Asc ao, desc ao, aa, sc, car, ia	no	MRI aorta: asc ao, desc ao, aa, ia	No
11	pos/fem	yes: fem	Asc ao, desc ao, aa, sc, ia, fem	yes: fem	nd	Nd
12	nd	nd	Asc ao, desc ao, aa, sc	no	MRI aorta: asc ao, desc ao	No
13	neg/ -	no	-	no	MRI aorta: desc ao	No

ver: vertebral artery; car: carotid artery; ax: axillary artery; sc: subclavian artery; asc ao: ascending aorta; desc ao: descending aorta; aa: abdominal aorta; ia: iliac artery; fem: femoral artery; mes: mesenterial artery; tru co: coeliac trunc; ren: renal artery; nd: not done; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography.

ESR and CRP, myalgia and aged over 65. She was on steroid therapy (1mg prednisolone/kg bodyweight). On admission she had normal CRP and ESR. The MRI of the aorta revealed a minimal contrast enhancement of the descending aorta, but in the PET/CT there was neither increased FDG uptake nor wall thickening, accordingly. In the duplex ultrasound no halo sign of the carotids, temporal arteries and subclavian arteries could be found.

MRI/MRA of the aorta or whole body MRI was done in 10 patients and – as far as the imaging modalities are comparable – corresponded very well with the findings in the PET/CT (Table II). Duplex ultrasound was performed in 11 of the 13 patients and was positive (halo sign) in 9 of these patients at least at one site. Only two patients had a negative duplex ultrasound (Patient 3 and 13), both showing only low (SUV_{max} 1.9) or no increased FDG uptake, respectively. Stenosis of at least one of the involved vessels was seen in the complementary CT scan in 8 patients. All these stenoses could be found in the corresponding duplex ultrasound examinations, with flow acceleration in this area (Table II). The control group (2 males and 6 females, median age: 57 years) showed no typically pathologic long segmental FDG uptake in the vessel wall at all. The SUV_{max} in these patients was measured at the aortic arch and ranged from 1.4 to 2.3.

Discussion

PET/CT is a new imaging modality which combines the advantages of exact anatomical imaging of CT and metabolic imaging with PET. As most patients with the suspicion of a large vessel vasculitis present with unspecific symptoms PET/CT is an ideal tool to discover vascular inflammation as well as to detect additional diseases such as malignant tumours or infections. In our case series most patients with the diagnosis GCA had atypical extracranial symptoms which complicated the diagnosis. This again emphasises the need of reliable diagnostic modalities and underlines the findings of other groups who describe extracranial involvement in a high percentage of their GCA patients (1, 2).

There are few data on the characteristics of [^{18}F] FDG uptake in PET for large vessel vasculitis, all describing an increased FDG uptake especially of the thoracic aorta (12-17). Because of the thinness of the vessel wall the accuracy of measurement and the reproducibility is low - in contrast to measurement in malignant tumours. To date, only little is known about the clinical relevance of the quantitative assessment. More detailed studies on the accuracy of the quantification of SUV in vasculitis are necessary. The visually enhanced FDG uptake is important for the diagnosis. In 12 of our 13 patients visually increased uptake (Fig. 1) could be seen, hinting at an intensive inflammation of the respective vessel walls. Patient no. 13 with no increased uptake – despite slight enhancement in the MRA – and effective GC treatment served as a negative control. Eight patients examined for solid tumours where retrospectively evaluated as negative controls, too. In this group a wide variation of SUVs measured over the aortic arch (1.4 - 2.3) could be found. Beacause of the overlapping range of SUVs in vasculitis

Table III. Affected arteries and corresponding SUV, showing those arteries which could be visually detected as vasculitis.

Patient	Ascending aorta	Descending aorta	Abdominal aorta	Supraaortic arteries	Iliac arteries	Femoral arteries
1	+ (5.7)	+ (5.8)	+ (3.9)	+ (3.7)	-	-
2	+ (3.3)	-	+ (2.7)	-	+ (2.7)	-
3	+ (1.8)	+ (1.9)	+ (2.5)	-	+ (1.6)	-
4	+ (3.9)	+ (4.4)	+ (5.2)	+ (3.7)	+ (3.1)	+ (2.5)
5	+ (2.5)	+ (2.4)	-	+ (1.9)	-	-
6	+ (3.5)	+ (3.0)	+ (4.0)	+ (3.7)	+ (3.9)	+ (3.3)
7	+ (6.1)	+ (6.8)	+ (6.8)	+ (5.9)	+ (5.2)	+ (3.5)
8	+ (2.6)	+ (2.8)	-	+ (3.7)	+ (1.9)	-
9	+ (3.1)	+ (3.6)	-	+ (3.4)	-	-
10	+ (3.0)	+ (3.1)	+ (3.2)	+ (3.0)	+ (2.5)	-
11	+ (1.7)	+ (1.6)	+ (1.8)	+ (1.9)	+ (1.6)	+ (1.6)
12	+ (4.2)	+ (2.5)	+ (3.0)	+ (3.0)	-	-
13	-	-	-	-	-	-

+: typical increased FDG uptake; -: no increased FDG uptake; (): max. SUV

and control patients, a further discrimination between pathologic and normal was unsure. This underlines the importance of the qualitative assessment in addition to SUV measurement. Therefore, only experienced colleagues in nuclear medicine should use this method to diagnose large vessel vasculitis as definite diagnostic criteria have not yet been defined. As described above, the typical pattern with the long segmental or circular uptake, respectively was the criteria we used to decide whether it was vasculitis or not.

In our case series, eight of thirteen patients already had arterial stenosis due to inflammation. Effective treatment should be started before this probably irreversible stage of vasculitis is reached. Acute phase reactants alone appear to be insufficient to estimate disease activity, as those patients who already received therapy (steroids, methotrexate, azathioprine or cyclophosphamide) at the time of the PET/CT had low ESR and CRP but still showed inflammatory activity in the PET/CT and a typical "halo sign" in the duplex ultrasound. This emphasizes that serum markers do not always correlate well with vasculitic disease activity and the need for reliable diagnostic methods. PET/CT as a whole body scan covers all affected sites in a single session – with limitation only in the head region. Inflammatory activity can be detected and anatomical changes localised in the same session. [^{18}F] FDG PET has been shown to be the most sensitive imaging tool to depict inflammation. Meller *et al*. (21) proved that metabolic imaging is more sensitive and more reliable than MRA for the early diagnosis of aortitis and the monitoring of disease activity during immunosuppressive therapy and therefore should be used as the first line investigation.

A common alternative reason for increased FDG uptake in the vessel wall is activated atherosclerosis (23, 24). The complementary CT in the PET/CT scan gives additional information about the morphology, such as calcifications in the arterial wall, which would hint at atherosclerotic lesions. To confirm vasculitis clinical findings, laboratory and alternative imaging methods were used in our patients. As far as the modalities can be compared the findings in the MRI in 10/13 patients corresponded very well with the PET/CT, with a slight advantage for PET/CT which discovered more affected areas.

The duplex ultrasound examinations which were performed in parallel to PET/CT showed that, in the hands of an experienced sonographer, this method is able to discover inflammation in most of the accessible arteries. However, especially the thoracic aorta and the proximal subclavian artery are difficult or even impossible to evaluate by duplex ultrasonography because of their anatomical location (16, 19). As ultrasound is an inexpensive, non-invasive and widely available method and is ideal to confirm an early suspicion.

Of course, there are some limitations in this small study. The inhomogeneity of the patient population and the lack of biopsies could be criticised. However, all but one patient did not have signs of temporal arteritis and hence biopsy was not feasible. The data of MRA/MRI and whole body MRI could not be compared with judging whether one modality is superior to the other but they provided additional information and confirmed the diagnosis.

PET/CT can detect complications such as stenoses in parallel without additional examinations. As PET/CT is an expensive imaging method, further studies should focus on the prospective comparison of PET/CT with MRI/MRA and Duplex ultrasound. Our preliminary data hint at a slight superiority of PET/CT to duplex ultrasound, which is unable to detect inflammation in the thoracic aorta and proximal supraaortic arteries – although in most patients, peripheral arteries were also involved.

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