Vasa 2011; 40: 219–227
© 2011 by Hans Huber Publishers, Hogrefe AG, Bern
S. Förster et al., Volume 40, Issue 3, May 2011
DOI 10.1024/0301-1526/a000096

Patterns of extracranial involvement in newly diagnosed giant cell arteritis assessed by physical examination, colour coded duplex sonography and FDG-PET

S. Förster[2], F. Tato[1], M. Weiss[2], M. Czihal[3], A. Rominger[2], P. Bartenstein[2], M. Hacker[2] and U. Hoffmann[3]

[1]University Heart Center Hamburg, Hamburg, Germany
[2]Department of Nuclear Medicine, Ludwig-Maximilians University Hospital, Munich, Germany
[3]Division of Vascular Medicine, Ludwig-Maximilians University Hospital, Munich, Germany

Summary

Background: The clinical spectrum of giant cell arteritis (GCA) varies from classical temporal arteritis (TA) to generalized large vessel GCA (LV-GCA) and fever of unknown origin (FUO). Extent and distribution of extracranial involvement in these different presentations of GCA is not well known, and its detection may depend on the choice of vascular imaging.
Patients and methods: In 24 patients with newly diagnosed GCA we systematically evaluated the presence and distribution of extracranial involvement by physical examination, duplex sonography (DS), and FDG-PET. Analysis of FDG-PET results was performed in comparison with 18 age-matched control-subjects scanned for oncological indications.
Results: Initial clinical diagnosis was TA in 11 patients, LV-GCA in 8 patients, and FUO in 5 patients. Clinically detectable arterial obstruction was present in 2 patients (18 %) with TA (only upper extremity), all patients with LV-GCA (upper and lower extremities) and no patient with FUO. Upper and/or lower limb large vessel vasculitis was detectable by DS in 45 % of the patients with TA and in 100 % of the patients with LV-GCA or FUO. FDG-PET confirmed upper extremity involvement in all affected patients, but had a very low specificity for lower limb involvement due to concomitant arteriosclerosis in these elderly patients. Aortitis was detectable by FDG-PET in 27 % of patients with TA and 75–80 % of patients with LV-GCA or FUO.
Conclusions: The combination of thorough clinical examination and DS is able to detect symptomatic as well as asymptomatic large vessel involvement in a large proportion of patients with newly diagnosed GCA. Distribution and manifestation of large vessel involvement differs between classical TA and LVGCA or FUO. FDG-PET provided only limited additional information and did not change the clinical diagnosis in any patient.

Key words: Giant cell arteritis, large vessel vasculitis, fever of unknown origin, duplex scan, FDG-PET

Zusammenfassung

Extrakranielles Befallsmuster bei neu diagnostizierter Riesenzellarteriitis erfasst durch klinische Untersuchung, farbkodierte Duplexsonographie und FDG-PET
Hintergrund: Das klinische Erscheinungsbild der Riesenzellarteriitis (GCA) ist heterogen. Die Erkrankung kann sich sowohl als klassische Arteriitis temporalis (TA), als auch als primär extrakranielle Großgefäßvaskulitis (LV-GCA) oder als Fieber unklarer Genese (FUO) manifestieren. Bisherige Daten zu Häufigkeit und Verteilung der extrakraniellen Großgefäßvaskulitis bei unterschiedlichen Formen der GCA sind uneinheitlich und in hohem Maße abhängig von der verwendeten Untersuchungsmethode.
Patienten und Methoden: Bei 24 Patienten mit neu diagnostizierter GCA wurden Vorkommen und Verteilung einer extrakraniellen Beteiligung systematisch durch klinische Untersuchung, Duplexsonographie (DS) und FDG-PET untersucht. Die Auswertung der FDG-PET erfolgte im Vergleich zu 18 gleichaltrigen, aus onkologischer Indikation untersuchten Kontrollpersonen.
Ergebnisse: Die klinische Diagnose war TA bei 11 Patienten, LV-GCA bei 8 Patienten und FUO bei 5 Patienten. Klinisch manifeste arterielle Obstruktionen fanden sich bei 2 Patienten (18 %) mit TA (nur obere Extremität), allen Patienten mit LV-GCA und keinem Patienten mit FUO. Duplexsonographisch hatten 45 % der Patienten mit TA und 100 % der Patienten mit LV-GCA oder FUO typische Zeichen der Großgefäßvaskulitis an Arterien der oberen und/oder unteren Extremität. Die FDG-PET bestätigte bei allen duplexsonographisch positiven Patienten eine Beteiligung der Schulter- und Armarterien, hatte aber eine sehr niedrige Spezifität im Bereich der Beinarterien. In der FDG-PET hatten 27 % der Patienten mit TA und 75–80 % der Patienten mit LV-GCA oder FUO eine Aortitis.
Schlussfolgerungen: Durch die Kombination von gründlicher klinischer Untersuchung und DS lässt sich bei einem erheblichen Anteil von Patienten mit neu diagnostizierter GCA eine extrakranielle Beteiligung nachweisen. TA, LV-GCA und FUO unterscheiden sich in Häufigkeit, Verteilung und klinischer Manifestation der Großgefäßbeteiligung. Die FDG-PET brachte nur wenig Zusatzinformation und bei keinem Patienten führte diese Untersuchung zu einer Änderung der Diagnose.

Vasa 2011; 40: 219–227

Introduction

Giant cell arteritis (GCA) is the most common vasculitis of large and medium-sized arteries, affecting almost exclusively individuals over 50 years of age. Inflammation of cranial arteries leads to the classical clinical signs of GCA, such as tender and swollen temporal arteries (*temporal arteritis*), temporal headache, jaw claudication and visual loss [10, 21, 28]. Extracranial involvement was long believed to be rare and mostly restricted to the subclavian and axillary arteries [13, 14, 19]. Recent advances in vascular imaging have contributed to the recognition of GCA as a systemic large-vessel vasculitis [4]. Involvement of the aorta and of peripheral arteries of the upper and lower extremities has been shown to be more frequent than previously assumed [7, 25]. The clinical course of extracranial GCA is highly variable and ranges from asymptomatic involvement to extensive occlusive disease with limb-threatening peripheral ischemia [16, 24] or serious aortic complications [12, 18]. Some patients present only with non-specific signs of systemic inflammation, and GCA is an important differential diagnosis of fever of unknown origin (FUO) in elderly patients [15].

Diagnosis of extracranial GCA may be challenging, particularly in the absence of symptomatic arterial obstruction. Today, duplex-scan (DS) is the first-line, non-invasive technique for the detection of large-vessel vasculitis [1, 6, 22, 23]. Circular, hypoechogenic thickening of arterial segments with perivascular edema ("halo") is the sonographic hallmark of large-vessel vasculitis. However, sonographic findings may be difficult to interpret in severely arteriosclerotic arterial segments of the aorta, iliac, and femoropopliteal arteries. Furthermore, DS provides only limited information on disease activity.

[^{18}F]-Fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) is increasingly being used for the diagnosis of large-vessel vasculitis [6]. Enhanced vascular tracer uptake on FDG-PET has excellent sensitivity and specificity for the diagnosis of Takayasu arteritis [27]. Several studies have shown that FDG-PET is capable of detecting extracranial GCA [2, 4, 8, 26]. However, arteriosclerosis has also been shown to cause enhanced vascular FDG-uptake [2, 9, 11, 20]. This circumstance may limit the specificity of FDG-PET for vasculitis in the elderly GCA-patients. Moreover, FDG-PET was recently shown to be unreliable for the prediction of relapses in this patient population [4, 8]. Based on currently available data, FDG-PET has still to be considered an experimental procedure for the clinical management of GCA.

In the current study we present data on the extent and distribution of extracranial involvement in 24 patients presenting at our institution with newly diagnosed GCA. In this cohort we analyzed the additional contribution of FDG-PET to the diagnosis of extracranial GCA as compared to standard evaluation based on thorough physical examination, basic hemodynamic assessment of peripheral circulation and DS.

Patients and methods

Patients and control subjects

Between January 2004 and December 2008, 76 patients with GCA were seen at our institution. 65 patients underwent a complete clinical and duplex-sonographic work-up according to the protocol specified below. During a period of 29 months (from March 2006 to August 2008) we included FDG-PET in the work-up of patients with suspected large vessel vasculitis. From this database, we retrospectively identified 24 patients with newly diagnosed GCA in whom initial work-up included a complete clinical and duplex-sonographic work-up and FDG-PET.

The patients were 20 females and 4 males with a mean age of 69 years. Five patients were referred to our department by an ophthalmologist, 10 by a rheumatologist, 3 by a vascular surgeon, and 6 by an internist or a general practitioner. The indication for temporal artery biopsy was at the discretion of the attending physician and was performed in 15 patients. Temporal artery biopsy was usually not performed in patients with primarily extracranial large vessel vasculitis or FUO and normal temporal arteries on physical examination and DS. Histological confirmation of diagnosis was possible in 11 patients. In the remaining 13 patients diagnosis was based on clinical presentation, laboratory signs of systemic inflammation and typical duplexsonographic findings of the temporal and/or peripheral arteries.

A cohort of 18 age-matched control subjects (10 females, 8 males; mean age 66 years) was retrospectively selected from the clinical PET database of the Department of Nuclear Medicine. In these patients FDG-PET had been performed for suspected malignant disease. Exclusion criteria for the control subjects included FDG-positive malignancy, ever having received chemotherapy, or history of inflammation of unknown origin, sepsis, or vasculitis.

The anonymized, retrospective analysis of the presented clinical data was approved by the ethics committee of the Ludwig Maximilians University of Munich.

Study protocol

At the time of diagnosis of GCA all patients were seen by an experienced specialist in vascular medicine. During this initial visit all patients received a physical examination,

haemodynamic measurements and a DS as detailed below. FDG-PET was scheduled within a week of the initial presentation. If deemed necessary, corticosteroid treatment was initiated without delay. Control subjects were investigated by whole body FDG-PET according to the same protocol as used for GCA patients. Control subjects were not available for DS or detailed clinical examination for vascular disease.

Clinical examination: Any history of intermittent, upper- and lower-limb claudication, or of ischemic rest-pain was recorded. The physical examination included the careful palpation of all peripheral pulses and auscultation of the peripheral arterial bed. Bilateral ankle and brachial pressures were measured by cw-Doppler, and pulse volume recordings were taken at the level of the thigh, calf, foot and toes.

Duplex ultrasound: DS were performed in all patients by an experienced physician using a GE Logiq 9 Ultrasound System (General Electric Medical Systems, Milwaukee, Wisconsin, USA) equipped with 1.5 – 4.5 MHz, 2.5 – 8.0 MHz, and 4.5 – 13.0 MHz transducers. The following vascular regions were examined in all patients: extracranial carotid and vertebral arteries, subclavian, axillary and brachial arteries, abdominal aorta, iliac arteries, femoral and popliteal arteries. Arteries of the forearm and crural arteries were examined only in cases with clinical signs of arterial occlusions in these vascular regions. The following sonographic findings were considered positive for arterial involvement by GCA: 1. Stenosis of the artery by long, concentric, hypoechogenic thickening of the arterial wall. 2. Hypoechogenic occlusion of the artery with concentric, hypoechogenic thickening of the arterial wall in the adjacent arterial segments. 3. Long, smooth, concentric, hypoechogenic thickening of the arterial wall by more than 2.0 mm with perivascular halo, without haemodynamically significant stenosis of the lumen.

FDG-PET imaging: All patients and control subjects fasted for at least six hours prior to PET scanning and had normal serum glucose levels at the time of FDG injection (mean serum glucose GCA patients: 104 ± 25 mg/dl; mean serum glucose controls: 106 ± 17.3 mg/dl). Subjects received 5 MBq/kg FDG as an intravenous bolus injection, and were asked to rest in a quiet room. One hour after tracer infusion, subjects reclined in the tomography, and a whole-body emission recording was obtained with a Philips Allegro PET scanner (Philips Healthcare, Best, The Netherlands) in 3D-aquisition mode. A transmission scan with internal caesium-137 point sources was performed for attenuation correction. Transaxial images were reconstructed iteratively by a dedicated 3D-RAMLA algorithm.
PET images were analyzed by visual interpretation of coronal, sagittal and transverse slices by two experienced nuclear medicine physicians blinded to the ultrasound, clinical and laboratory data. Severity of large vessel FDG-uptake of GCA patients and control subjects in paired (right and left side) subclavian, axillary, brachial and carotid artery (upper limb), and iliacal, femoral and popliteal artery (lower limb) and in the thoracic aorta was visually graded using a conventional four-point scale [5], in relation to individual mean liver uptake (see Figure 1) as follows: 0 = no uptake; 1 = low-grade uptake (lower than liver uptake); 2 = intermediate-grade uptake (similar to liver uptake); 3 = high-grade uptake (higher than liver uptake).
Interobserver agreement regarding the FDG-uptake scoring was obtained in 41 of 43 patients / control subjects (95.3 %), whereas the intraobserver reproducibility was 40 of 43 (93.0 %).

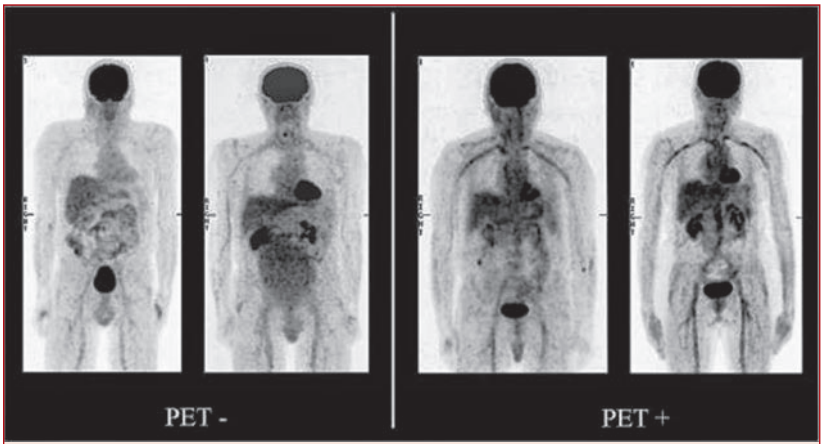

Figure 1: Semi-quantitative scoring system showing whole-body PET scans of patients with no and low-grade (PET-) vascular FDG-uptake (grades 0 and 1) and patients with intermediate-grade and high-grade (PET+) vascular FDG-uptake (grades 2 and 3).

Statistical analysis

All data are given as mean ± SD unless stated otherwise. All statistical testing was performed with SPSS software, version 13.0 (SPSS, Chicago, IL, USA). CRP levels of GCA patients and control subjects were compared using the unpaired t-test. For further statistical analysis, the grade of FDG vessel up-

Vasa 2011; 40: 219 – 227

take was categorized in a dichotomous way designated PET– for grade 0 or 1 and PET+ for grade 2 or 3. Results were tabulated for calculation of sensitivity, specificity, negative predictive value, and positive predictive value.

Results

Clinical characteristics of GCA patients and controls are summarized in Table I. Reasons for initial presentation were clinical signs of cranial (temporal) arteritis (e. g. headache, jaw claudication, visual loss, polimyalgia rheumatica) in 11 patients, symptoms of peripheral ischemia in 8 patients (upper limb only in 2, upper and lower limb in 4, and lower limb only in 2 patients), and fever and/or systemic inflammation of unknown origin (FUO) in 5 patients. Of the 10 patients presenting with symptomatic peripheral ischemia (2 in the temporal arteritis group and 8 in the primarily extracranial group), 8 had symptoms of upper and/or lower limb claudication, and two patients had critical ischemia of the legs requiring surgical revascularization for limb salvage.

The 11 patients with AT and 4 of the 8 patients with LV-GCA were specifically referred to our department because of suspected GCA. The other 4 patients with LV-GCA were referred to our department because of peripheral ischemia. The 5 patients with FUO were referred to us by our rheumatology department for DS of large arteries. The FDG-PET was performed in 3 patients after and in 2 patients before DS.

At the time of FDG-PET 5 patients were still untreated. 19 patients had been started on 60 to 80 mg of prednisone 1 to 8 days before. Only one patient had been on prednisone for 28 days and was taking 20 mg at the time of investigation.

Temporal artery biopsy was performed in 15 patients and was positive in 10. The two patients with critical limb ischemia had a positive biopsy of the occluded superficial femoral artery acquired during bypass surgery. DS of the temporal artery was performed in 21 patients and was positive in 12. In the 14 patients who had temporal artery duplex and biopsy both were positive in 9 and both were negative in 2 patients. Three patients had positive duplex results but a negative biopsy, and we had no false negative duplex result. As compared to biopsy, temporal artery DS had a positive predictive value of 75 % and a negative predictive value of 100 %. Based on biopsy and/or DS the temporal arteries were involved in 13 of 24 patients (54 %). The frequency of temporal arteritis detected by ultrasound and/or biopsy was 91 % in patients presenting with typical cranial GCA, but only 25 % in patients with primarily extracranial GCA, and 20 % in FUO (Table II).

Table II shows age, CRP values and the results of clinical examination, DS and FDG-PET in the three clinical presentations of GCA patients. Patients with FUO tended to be younger and to have higher levels of systemic inflammation than the other two groups. In 11 patients presenting with typical cranial GCA we found two cases with extracranial involvement in the axillary arteries detectable by physical examination and ultrasound. In this group, DS detected 4 additional cases of clinically unapparent involvement of lower limb arteries. In 8 patients presenting primarily with symptomatic and clinically apparent extracranial involvement, DS confirmed the finding in each case (2 upper limbs, 2 lower limbs and 4 upper and lower limbs). In addition, DS revealed two upper extremity and one lower extremity involvement not detectable by clinical examination. The five patients presenting with FUO did not have any arterial findings detectable on physical examination. However, all of them had pathological results on DS (one only lower limbs, one upper and lower limbs and three only upper limbs).

In all three patient groups upper limb FDG-PET results correlated well with clinical and sonographic findings (Table II). Only one patient in the cranial GCA group had a positive upper limb FDG-PET result not detectable by DS. In the lower limbs we observed an exceptionally high rate of positive FDG-PET results in all groups of GCA patients (82 – 100 %), and we found no relationship between FDG-uptake and clinical or sonographic findings.

Table I: Clinical characteristics of 24 patients with giant cell arteritis and 18 control subjects.

	Patients (n = 24)	Controls (n = 18)
Sex (female / male)	20 / 4	10 / 8
Age, years (mean ± SD, range)	69 ± 9, 53 – 87	67 ± 10, 49 – 85
Serum CRP (mg/dl ± SD, reference range < 0.5)	5.8 ± 4.5	0.6 ± 1.3
Patients on glucocorticosteroid treatment	19 (79%)	0
Days on glucocorticoid treatment (mean ± SD)	5.7 ± 6.3	0
Histological confirmation of GCA	11 (46%)	0

GCA = giant cell arteritis

Table II: Patterns of involvement in patients with different clinical presentations of giant cell arteritis

	TA (n = 11) n (%)	LV-GCA (n = 8) n (%)	FUO (n = 5) n (%)
Age (mean ± SD)	74 ± 8	67 ± 4	58 ± 4
CRP (mean ± SD)	4.4 ± 4.2	4.8 ± 3.3	10.6 ± 4.0
Temporal artery involved by biopsy and/or duplex	10 (91)	2 (25)	1 (20)
UE clinical involvement	2 (18)	6 (75)	0
UE sonographic involvement	2 (18)	7 (88)	4 (80)
UE FDG-PET positve	3 (27)	6 (75)	4 (80)
LE clinical involvement	0	6 (75)	0
LE sonographic involvement	4 (36)	6 (75)	2 (40)
LE FDG-PET positve	9 (82)	8 (100)	5 (100)
Aorta FDG-PET positive	3 (27)	6 (75)	4 (80)

Abbreviations: TA: temporal arteritis, LV-GCA: large vessel giant cell arteritis, FUO: fever of unknown origin, TA temporal artery, UE: upper extremity, LE: lower extremity, FDG-PET: [18F]-Fluoro-2-deoxy-D-glucose positron emission tomography.

Table III: Accuracy of FDG-PET compared to duplex sonography for the detection of vascular inflammation of the upper limb vessels in 24 patients with GCA (left), and frequency of vascular FDG-uptake in the upper limb vessels of 18 control subjects (right)

Upper limb	GCA patients n = 24		Control subjects n = 18
	DS –	DS +	
PET–	10	1	18
PET+	1	12	0
Sensitivity:	92%	Specificity:	91%
Positive predictive value:	92%	Negative predictive value:	91%

Table IV: Accuracy of FDG-PET compared to duplex sonography for the detection of vascular inflammation of the lower limb vessels in 24 patients with GCA (left), and frequency of vascular FDG-uptake in the lower limb vessels of 18 control subjects (right)

Lower limb	GCA patients n = 24		Control subjects n = 18
	DS –	DS +	
PET–	1	1	18
PET+	12	10	8
Sensitivity:	91%	Specificity:	8%
Positive predictive value:	45%	Negative predictive value:	50%

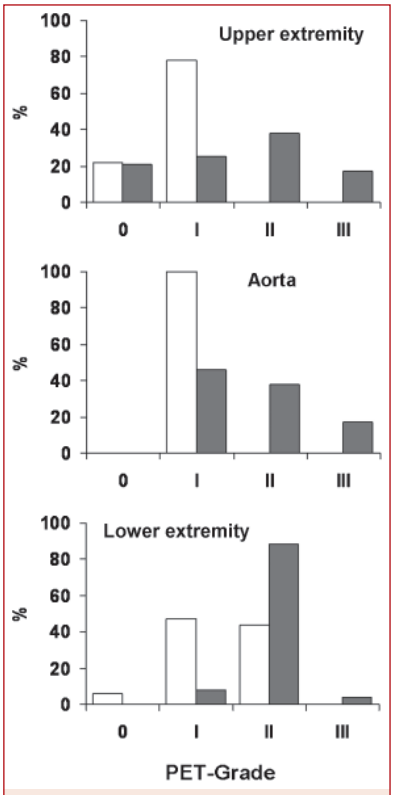

Figure 2: Distribution of the intensity of FDG-uptake in different vascular regions of 24 patients with newly diagnosed giant cell arteritis (gray bars) and 18 control subjects (white bars).

In the whole cohort of GCA patients FDG-PET had a sensitivity and specificity of more than 90 % for the detection of upper limb involvement as compared to DS. Good specificity in this vascular region is supported by the lack of FDG-uptake in upper limbs of the 18 control subjects (Table III).

Positive lower limb FDG-PET results were found in 22 of 24 GCA patients (Table IV). This high rate of FDG-uptake resulted in very low specificity of FDG-PET for the detection of lower limb involvement as compared to DS. The high rate of FDG uptake in the lower limbs of control subjects (8 positive FDG-PET results, 44 %), confirms a low specificity for large vessel vasculitis in this age group.

Detection of aortic involvement by FDG-PET was common in our GCA patients (Table II). Aortic FDG-uptake was graded positive in 13 of 24

Vasa 2011; 40: 219–227

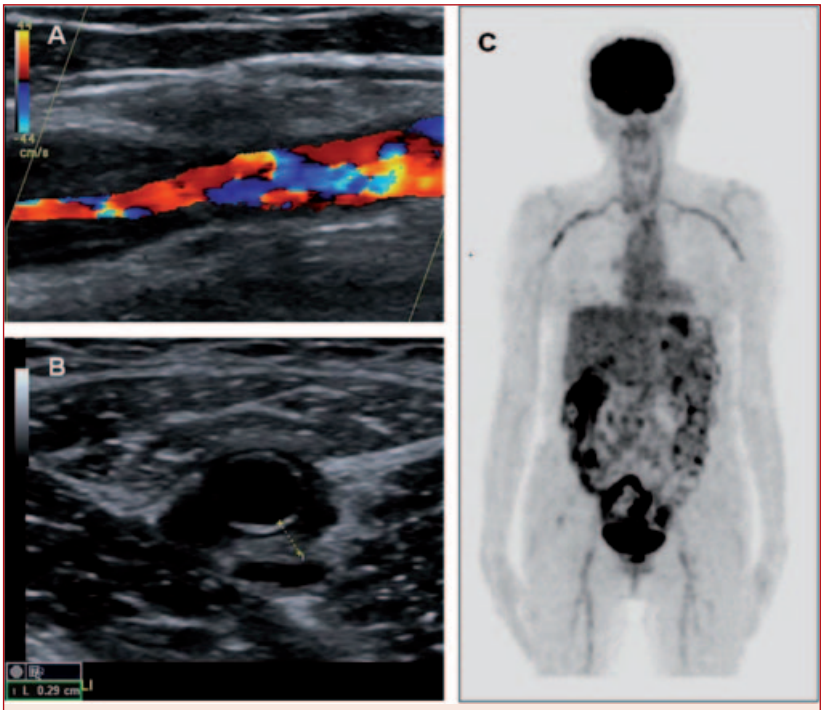

Figure 3: Typical vascular findings in extracranial GCA. Panel A: duplex scan of the left axillary artery of a 68 years old male with severely symptomatic, extracranial GCA of upper and lower limbs. The longitudinal section shows segmental stenosis of the axillary artery due to marked, hypoechogenic, concentric thickening of the arterial wall. Panel B: duplex scan of the right superficial femoral artery of a 57 years old female with FUO. The cross-section shows non-occlusive, circular, hypoechogenic wall thickening. Panel C: whole-body FDG-PET of a 75 years old female with typical cranial arteritis and bilateral stenosis of the axillary artery on duplex scan. FDG-PET shows grade 3 uptake in the subclavian- and axillary arteries, as well as asymptomatic and probably non-specific grade 2 uptake in the femoral arteries.

patients (54 %). The frequency of aortic involvement was highly dependent on the clinical presentation of the patients (27 % in cranial GCA, 75 % in extracranial GCA and 80 % in FUO). The distribution of FDG-PET grades in GCA patients and controls is shown in Figure 2. For all vascular regions we observed a shift of FDG-uptake to higher values in GCA patients. In the upper extremities and in the aorta we observed no overlap between the pathological (grade 2 and 3) findings in GCA and the normal (grade 0 and 1) findings in the controls. In the lower limbs however, we observed considerable overlap of grade 2 findings in patients and controls. A grade 3 lower extremity FDG-PET result was observed in only one GCA patient.

Two representative duplexsonographic images of GCA involvement of the axillary and femoral arteries, and a typical FDG-PET scan in a patient with temporal arteritis and upper limb involvement are shown in Figure 3.

Discussion

In our patients with newly diagnosed GCA we observed a high rate of extracranial involvement. Of 24 patients only 9 (38 %) had classical cranial GCA without symptomatic vasculitis of peripheral arteries. Two patients had typical temporal arteritis and symptomatic stenosis of the axillary arteries, 8 patients had primarily extracranial large vessel vasculitis with symptomatic upper and/or lower limb ischemia, and 5 patients had non-obstructive extracranial large vessel vasculitis presenting only with systemic inflammation and FUO. Patients with symptomatic limb ischemia are more likely to be referred to a department for vascular medicine than patients presenting only with classical temoral arteritis or polymyalgia rheumatica. Consequently, the patients seen at our institution are probably not representative of the more common patients usually seen by rheumatologists and ophthalmologists. Nevertheless, our data clearly support the concept, that GCA is a systemic large-vessel vasculitis capable of producing serious vascular symptoms and complications in a clinically significant subset of patients. In our subgroup of patients presenting with typical temporal arteritis the rate of symptomatic and asymptomatic extracranial involvement detected by physical examination or DS was 45 % (5 out of 11).

Involvement of the subclavian and axillary arteries and of the aortic arch is the best known manifestation of extracranial GCA [13, 14, 19]. Involvement of the lower limb arteries is considered unusual [16, 24]. This preferential involvement of the upper limb arteries could not be confirmed in the spectrum of patients seen at our institution. In 10 patients with symptomatic extracranial GCA the affected arterial segments involved only the upper limbs in 4, only the

lower limbs in 2, and both upper and lower limbs in 4.

The high rate of lower limb involvement observed in this study may be due to the particular spectrum of large-vessel vasculitis seen at our institution. 8 of our 24 patients presented with a primarily extracranial large vessel vasculitis without the typical clinical features of cranial artery involvement (only 25 % had positive temporal artery duplex or biopsy in this subgroup). These patients displayed an aggressive, obliterating extracranial vasculitis with equally high rates of symptomatic involvement in the upper- and lower limb arteries and 75 % also had aortitis on FDG-PET (Table II). Our results in this subgroup of patients are in line with a similar cohort of patients with histologicaly documented extracranial GCA from the Mayo Clinic [16]. Also this study found an almost equal distribution of the arterial involvement between upper and lower limbs (39 % aortic arch, 26 % subclavian and axillary arteries, 18 % femoropopliteal arteries) in a cohort of patients with a low rate of temoral artery involvement (25 %). Similarly, in the recent study by Aschwanden et al. [1] large vessel vasculitis was detected by DS in 12 of 38 (32 %) patients with GCA, and was almost equally distributed between upper and lower limbs.

The distribution and presentation of extracranial involvement was different in our 11 patients with typical cranial arteritis. In this subgroup we found only two cases with symptomatic upper limb involvement, whereas all 4 cases of femoropopliteal involvement were non-obstructive and asymptomatic. Aortitis was present on FDG-PET in 27 % of these patients. This observation suggests that extracranial involvement is less frequent and more localized in this subgroup. Moreover, the apparent predominance of upper limb involvement reported in cranial arteritis may in fact be due to a higher rate of asymptomatic involvement in the lower limb arteries. In our experience, patients with temporal arteritis frequently have concentric wall thickening in the femoropopliteal arteries without luminal narrowing. This manifeststion of GCA usually remains totally asymptomatic and is only detectable on DS. An example for this pattern is shown in Figure 3.

GCA may also present as a syndrome of systemic inflammation and fever (FUO) without clinically evident vascular symptoms [15]. We observed this clinical presentation in 5 of our 24 patients. Only one of these patients had a positive sonographic finding in the temporal arteries, which could not be confirmed by biopsy. However, all patients had asymptomatic involvement of peripheral arteries on DS (3 only upper limbs, 1 upper and lower limbs, 1 only lower limbs).

A further objective of the present study was to investigate the contribution of FDG-PET in the initial work-up of newly diagnosed GCA. By detecting increased metabolic activity in the inflamed arterial wall, FDG-PET has the potential to recognize large vessel vasculitis on a whole-body basis very early in the course of the disease [6]. FDG-PET has been shown to have excellent sensitivity and specificity for the diagnosis of Takayasu arteritis [27]. Extracranial GCA is also detectable by FDG-PET [2, 4, 6, 8, 26]. Increased vascular FDG uptake due to arteriosclerosis may however reduce the specificity of FDG-PET in the elderly population usually affected by GCA [2, 9, 11, 20]. In our study we observed excellent agreement between duplex ultrasound and FDG-PET in the subclavian and axillary arteries with positive and negative predictive values above 90 %. No control subject had a grade 2 or 3 pathological tracer uptake in the upper limb arteries, probably reflecting the low rate of advanced arteriosclerosis in this vascular region. This finding supports a high specificity of increased FDG-uptake for vasculitis in the upper limb arteries. Our results suggest similar sensitivities for FDG-PET and Duplex sonographiy in the upper limbs. Only one GCA patient had a positive PET result in the upper limb arteries without signs of vasculitis already detectable by physical examination or DS.

A pathological FDG-uptake in the lower limb arteries was seen in 22 out of 24 GCA patients (92 %) but also in 8 out of 18 age-matched controls (44 %). The distribution of FDG-PET results showed a shift towards higher values in GCA for all studied vascular regions (figure 2). However, we observed a high rate of overlap between patients and controls in the lower limb arteries. The intensity and pattern of distribution of lower limb FDG-uptake was indistinguishable between vasculitis patients and controls with unspecific (probably arteriosclerotic) vascular uptake. The low specificity of elevated FDG-uptake for the diagnosis of vasculitis in the lower limb arteries is confirmed by the lack of correlation between FDG-PET results and duplexsonographic findings. In 12 of 22 patients with positive lower extremity PET, we were not able to detect any sign of vasculitis by duplex ultrasound. All these patients had some degree of femoropopliteal arteriosclerosis on DS.

Our data suggest that for the initial diagnosis of peripheral, extracranial GCA, stand-alone FDG-PET provides only limited additional information in the upper limb arteries and is highly unreliable in the lower limb arteries. New generation scanners combining FDG-PET with computed tomography (PET-CT) allow improved anatomic assignment, and simultaneous imaging of arteriosclerotic plaques and calcifications [20]. Due to these improvements, PET-CT may achieve a higher specificity for

Vasa 2011; 40: 219 – 227

vasculitis in arterial segments with concomitant arteriosclerosis. Future studies will have to clarify the role of PET-CT for the initial diagnosis of large vessel vasculitis.

FDG-PET may be more valuable for the follow-up of inflammatory activity during treatment in cases with contradicting clinical and laboratory findings. However, also this indication is controversial [4, 8] and has to be validated in larger clinical studies.

An undisputed advantage of FDG-PET is the ability to detect inflammation in vascular regions not readily accessible for high-resolution ultrasound. This is particularly important for the diagnosis of aortitis. In our cohort 13 out of 24 patients (54 %) had a positive PET result in the thoracic and/or abdominal aorta. Unlike in the iliac and femoropopliteal region, we found a high specificity of grade 2 or 3 FDG-PET results for aortitis in GCA patients. No control patient had a positive grade 2 or 3 PET result in the aorta (figure 2). Asymptomatic aortitis was detected in 27 % of our patients with isolated temporal arteritis and in 75 – 80 % of patients presenting with symptomatic extracranial large vessel vasculitis or FUO. Again, this finding supports the concept that classical, usually localized temporal arteritis has to be distinguished from a more generalized form of large vessel vasculitis with a much higher rate of both peripheral and aortal involvement.

These findings suggest a role of FDG-PET in the early diagnosis of large vessel vasculitis with aortic involvement in patients who do not yet have clinically apparent vascular symptoms. These patients may present with signs of systemic inflammation and non-specific general symptoms or with FUO. FDG-PET already plays an important role in diagnostic algorithms for the differential diagnosis of FUO [3], and large vessel vasculitis is one of several frequent causes of FUO detectable by FDG-PET. However, our data also show that most patients with clinically not apparent large vessel vasculitis or FUO have typical signs of large vessel vasculitis when carefully studied by DS of the peripheral arteries. Venous DS is already part of published diagnostic algorithms for FUO [17]. We suggest that arterial DS should also be included early in the diagnostic work-up of these patients. We have shown that extracranial large vessel involvement is frequent in GCA, and my cause serious vascular complications. Our results highlight the pivotal role of a thorough vascular examination by an expert physician and DS for the detection of large vessel involvement in GCA. The role of FDG-PET in the clinical management of these patient remains to be defined. For the initial evaluation of these patients, FDG-PET provides only very limited additional information. An exception may be the early diagnosis of aortitis in patients with otherwise normal vascular findings and negative DS.

Conflicts of interest

There are no conflicts of interest existing.

References

1 Aschwanden M, Kesten F, Stern M, Thalhammer C, Walker UA, Tyndall A, Jaeger KA, Hess C, Daikeler T. Vascular involvement in patients with giant cell arteritis determined by duplex sonography of 2x11 arterial regions. Ann Rheum Dis 2010; 68: 1356 – 9.

2 Blockmans D, Stroobants S, Maes A, Mortelmans L. Positron emission tomography in giant cell arteritis and polymyalgia rheumatica: evidence for inflammation of the aortic arch. Am J Med 2000; 108: 246 – 9.

3 Blockmans D, Knockaert D, Maes A, De Caestecker J, Stroobants S, Bobbaers H, Mortelmans L. Clinical value of [^{18}F]fluorodeoxyglucose positron emission tomography for patients with fever of unknown origin. Clin Infect Dis 2001; 32: 191 – 6.

4 Blockmans D, De Ceuninck L, Vanderschuren S, Knockaert D, Mortelmans L, Bobbaers H. Repetitive 18F-Fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. Arthritis Rheum 2006; 55: 131 – 7.

5 Blockmans D, Coudyzer W, Vanderschueren S, Stroobants S, Loeckx D, Heye S, De Ceuninck L, Marchal G, Bobbaers H. Relationship between fluorodeoxyglucose uptake in the large vessels and late aortic diameter in giant cell arteritis. Rheumatology (Oxford) 2008; 47: 1179 – 84.

6 Blockmans D, Bley T, Schmidt W. Imaging for large-vessel vasculitis. Curr Opin Rheumatol 2009; 21: 19 – 28.

7 Bongartz T, Matteson EL. Large-vessel involvement in giant cell arteritis. Curr Opin Rheumatol 2006; 18: 10 – 7.

8 Both M, Ahmadi-Simab K, Reuter M, Dourvos O, Fritzer E, Ullrich S, Gross WL, Heller M, Bähre M. MRI and FDG-PET in the assessment of inflammatory aortic arch syndrome in complicated courses of giant cell arteritis. Ann Rheum Dis 2008; 67: 1030 – 3.

9 Bural GG, Torigian DA, Chamroonrat W, Houseni M, Chen W, Basu S, Kumar R, Alavi A. FDG-PET is an effective imaging modality to detect and quantify age-related atherosclerosis

in large arteries. Eur J Nucl Med Mol Imaging 2008; 35: 562 – 9.
10 Caspary L. Vasculitides of the large vessels. Vasa 2011; 40: in press.
11 Chen W, Bural GG, Torigian DA, Rader DJ, Alavi A. Emerging role of FDG-PET/CT in assessing atherosclerosis in large arteries. Eur J Nucl Med Mol Imaging. 2009; 36: 144 – 51.
12 Evans JM, O'Fallon WM, Hunder GG. Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis: a population-based study. Ann Intern Med 1995; 122: 502 – 7.
13 Hunder GG, Ward LM, Burbank MK. Giant-cell arteritis producing an aortic arch syndrome. Ann Intern Med 1967; 66: 578 – 82.
14 Klein RG, Hunder GG, Stanson AW, Sheps SG. Large artery involvement in giant cell (temporal) arteritis. Ann Intern Med 1975; 83: 806 – 12.
15 Knockaert DC, Vanderschueren S, Blockmans D. Fever of unknown origin in adults: 40 years on. J Intern Med 2003; 253: 263 – 75.
16 Lie JT. Aortic and extracranial large vessel giant cell arteritis: a review of 72 cases with histopathological documentation. Semin Arthritis Rheum 1995; 24: 422 – 31.
17 Mourad O, Palda V, Detsky A. A comprehensive evidence-based approach to fever of unknown origin. Arch Intern Med 2003; 163: 545 – 51.
18 Neunninghoff DM, Hunder GG, Christianson TJH, McClelland RL, Matteson EL. Incidence and predictors of large-artery complications (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. Arthritis Rheum 2003; 48: 3522 – 31.
19 Perruquet JL, Davis DE, Harrington TM. Aortic arch arteritis in the elderly. Arch Intern Med 1986; 146: 289 – 91.
20 Rominger A, Saam T, Wolpers S, Cyran CC, Schmidt M, Foerster S, Nikolaou K, Reiser MF, Bartenstein P, Hacker M. ^{18}F-FDG PET/CT identifies patients at risk for future vascular events in an otherwise asymptomatic cohort with neoplastic disease. J Nucl Med 2009; 50: 1611 – 20.
21 Salvarani C, Cantini F, Boiardi L, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. N Engl J Med 2002; 347: 261 – 71.
22 Schmidt WA, Natusch A Moeller DE, Vorpahl K, Gromnika-Ihle EJ. Involvement of peripheral arteries in giant cell arteritis: a color Doppler sonography study. Clin Exp Rheumatol 2002; 20: 309 – 18.
23 Schmidt WA, Seifert A, Gromnica-Ihle E, Krause A, Natusch A. Ultrasound of proximal upper extremity arteries to increase the diagnostic yield in large-vessel giant cell arteritis. Rheumatology 2008; 47: 96 – 101.
24 Tatò F, Hoffmann U. Clinical presentation and vascular imaging in giant cell arteritis of the femoro-popliteal and tibio-peroneal arteries. J Vasc Surg 2006; 44: 176 – 82.
25 Tatò F, Hoffmann U. Giant cell arteritis: a systemic vascular disease. Vasc Med 2008; 13: 127 – 40.
26 Turlakow A, Yeung HWD, Pui J, Macapinlac H, Liebovitz E, Rusch V, Goy A, Larson SM. Fludeoxyglucose positron emission tomography in the diagnosis of giant cell arteritis. Arch Intern Med 2001; 161: 1003 – 7.
27 Webb M, Chambers A, Al-Nahhas A, Mason JC, Maudlin L, Rahman L, Frank J. The role of ^{18}F-FDG PET in characterising disease activity in Takayasu arteritis. Eur J Nucl Med Mol Imaging 2004; 31: 627 – 34.
28 Weyand CM, Goronzy JJ. Giant-cell arteritis and polymyalgia rheumatica. Ann Intern Med 2003; 139: 505 – 15.

Correspondence address

Prof. Federico Tato, MD
Vascular Medicine
University Heart Center Hamburg
Martinisrasse 52
DE-20246 Hamburg
Germany
E-mail: f.tato@uke.de

Submitted: 18.09.2010
Accepted after revision: 12.11.2010