European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:184–193
https://doi.org/10.1007/s00259-018-4106-0

ORIGINAL ARTICLE

# Simple dichotomous assessment of cranial artery inflammation by conventional 18F-FDG PET/CT shows high accuracy for the diagnosis of giant cell arteritis: a case-control study

Berit Dalsgaard Nielsen[1,2] · Ib Tønder Hansen[1,2] · Stine Kramer[3] · Ate Haraldsen[3] · Karin Hjorthaug[3] · Trond Velde Bogsrud[3] · June Anita Ejlersen[4] · Lars Bjørn Stolle[5] · Kresten Krarup Keller[1] · Philip Therkildsen[1,2] · Ellen-Margrethe Hauge[1,2] · Lars Christian Gormsen[3]

Received: 18 May 2018 / Accepted: 18 July 2018 / Published online: 31 July 2018


## Abstract

**Purpose** To estimate the diagnostic accuracy of conventional 18F-FDG PET/CT of cranial arteries in the diagnosis of giant cell arteritis (GCA).

**Methods** The study was a retrospective case-control study. The reference diagnosis was fulfillment of the 1990 ACR criteria for GCA. All patients had new-onset GCA. Conventional 18F-FDG PET/CT was performed before glucocorticoid treatment. Controls were age- and sex-matched patients with a previous history of malignant melanoma (MM) undergoing surveillance PET/CT >6 months after MM resection. PET images were evenly cropped to include only head and neck and were assessed in random order by four nuclear medicine physicians blinded to reference diagnosis. Temporal (TA), maxillary (MA) and vertebral (VA) arteries were visually rated for 18F-FDG uptake. Interreader agreement was evaluated by Fleiss kappa.

**Results** A total of 44 patients and 44 controls were identified. In both groups, the mean age was 69 years ($p = 0.45$) and 25/44 were women. 35/41 GCA patients were temporal artery biopsy positive (TAB). Considering only FDG uptake in TA and/or MA, diagnostic sensitivity and specificity was 64 and 100%. Including VA, sensitivity increased to 82% and specificity remained 100%. Interreader agreement was 91% and Fleiss kappa 0.82 for the PET diagnosis based on the cranial arteries.

**Conclusion** Conventional 18F-FDG PET/CT is an accurate and reliable tool to diagnose cranial arteritis in glucocorticoid-naïve GCA patients. The high diagnostic specificity suggests that TAB can be omitted in patients with 18F-FDG uptake in cranial arteries. 18F-FDG PET/CT performed in patients with suspected vasculitis should always include the head and neck.

**Keywords** Giant cell arteritis · 18F-FDG PET/CT · Diagnostic accuracy · Interreader agreement

## Introduction

Previously, giant cell arteritis (GCA) was primarily considered a cranial disease, presenting with new-onset headache, jaw claudication and/or visual disturbances. With the emergence of new diagnostic imaging modalities, the systemic nature of GCA with widespread large- and medium vessel involvement, and thus a wider spectrum of clinical phenotypes, is appreciated.

Conventionally, temporal artery biopsy (TAB) has been mandatory in GCA diagnosis and, although only moderately sensitive [1, 2], it has been considered the reference standard [3]. However, the TAB histology result is usually not available until weeks after treatment initiation, and the biopsy outcome only seldom alters disease management [4]. This emphasizes

✉ Berit Dalsgaard Nielsen
bernil@rm.dk

1 Department of Rheumatology, Aarhus University Hospital, Nørrebrogade 44, bygning 3, 8000 Aarhus, Denmark

2 Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

3 Department of Nuclear Medicine and PET Centre, Aarhus University Hospital, Aarhus, Denmark

4 Department of Nuclear Medicine, The Regional Hospital West Jutland, Herning, Denmark

5 Department of Plastic and Breast Surgery, Aarhus University Hospital, Aarhus, Denmark

the need for accurate and promptly available confirmatory diagnostic tests in GCA.

The recent *EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice* advises that an early diagnostic imaging test is performed in all patients suspected of GCA to confirm diagnosis [5]. Fluorine-18-fluorodeoxyglucose (18F-FDG) positron emission tomography/CT (PET) can be used for the confirmation of extracranial large vessel GCA (LV-GCA), e.g., arteritis involving the aorta and its main branches, in which it has proven high diagnostic accuracy [5–9]. Vascular ultrasound (US) is recommended for the assessment of GCA in cranial arteries, provided the sonographer is adequately skilled and the examination is promptly available. Due to USs high positive predictive value, a TAB is considered unnecessary in patients with either high or low clinical probability of GCA and a matching US result. In contrast, 18F-FDG PET/CT is not recommended for the assessment of inflammation in cranial arteries [5], although 18F-FDG uptake in inflamed cranial arteries in GCA patients has occasionally been reported [10–12].

In GCA, accurate diagnostic tools are needed to establish a reliable diagnosis. The numerous phenotypical GCA presentations make the diagnostic process challenging, and diagnosis is often delayed. False negative diagnostic tests may delay glucocorticoid treatment, increasing the risk of vascular complications such as vision loss. A false positive diagnosis encourages unnecessary, long-lasting glucocorticoid treatment with frequent and potentially serious side effects.

In new-onset GCA patients, 18F-FDG uptake in cranial arteries could indicate inflammation and, therefore, serve as an adjunct diagnostic tool. The aim of this case-control study was to evaluate diagnostic accuracy of conventional 18F-FDG PET/CT to detect cranial artery inflammation leading to a diagnosis of GCA.

## Material and methods

### Study design

A retrospective case-control study was conducted at Department of Rheumatology and Department of Nuclear Medicine & PET Center, Aarhus University Hospital, Denmark.

### Participants

#### Cases

Since October 2014 all glucocorticoid-naïve patients suspected of new-onset GCA referred to the Department of Rheumatology at Aarhus University Hospital have been considered for inclusion in an observational cohort. Patients give their informed consent to have blood samples for a bio-bank and for the use of clinical, laboratory, imaging and histology data for research purposes.

18F-FDG PET/CT is readily available in our institution (usually within 1 working day) and is included in the routine diagnostic evaluation of GCA suspected patients. The 18F-FDG PET/CT can usually be planned by the time of referral, allowing for pre-treatment PET in many GCA suspected patients not presenting with unequivocal cranial symptoms of GCA. Other patients with PET suggestive of LV-GCA are referred from other departments for confirmation of diagnosis and commencement of treatment. Treatment is initiated without delay in patients with unequivocal cranial symptoms of GCA. Patients without a pre-treatment 18F-FDG PET/CT were not considered for inclusion in the cohort.

For the purpose of this study, we included patients from the cohort fulfilling the following criteria: (1) clinically diagnosed with new-onset GCA before December 2017 and fulfilling the 1990 ACR classification criteria for GCA [13]; and (2) diagnosis confirmed at the 6 months follow-up visit. We excluded patients in whom the 18F-FDG PET/CT did not include the head and neck.

#### Controls

As controls, we included subjects undergoing routine surveillance 18F-FDG PET/CT as part of the recommended follow-up of patients with high risk malignant melanoma (MM) between October 2013 and December 2017. 18F-FDG PET/CTs performed ≤6 months after MM resection, 18F-FDG PET/CTs revealing recurrent or new cancer and controls with a medical record exhibiting a history of PMR or GCA, were excluded. Controls were matched to the GCA patients by gender and age (± 3 years) by the time of the PET scan. To reflect the referral pattern in a tertiary hospital, we matched GCA and controls one to one. Eligible controls who had several 18F-FDG PET/CT scans were matched with one GCA patient only.

### Reference diagnosis and index test

#### Reference diagnosis

Fulfilment of the 1990 ACR criteria for GCA was considered reference diagnosis [13]. Medical history, physical examination, laboratory and imaging tests were performed before treatment was initiated in all GCA patients. Patients were referred for a TAB, which was considered positive in the presence of an inflammatory infiltrate in any vessel wall layer. All test results were evaluated by an experienced rheumatologist to establish the diagnosis and to confirm eligibility criteria.

### 18F-FDG PET/CT procedure

Conventional whole-body 18F-FDG PET/CT was performed according to institution protocols using combined PET/CT scanners. Two different PET systems were used: GE Discovery 690 (GE Healthcare, Chicago, IL, U.S.A.) (19 cases) and Siemens Biograph 64 (Siemens Healthcare, Erlangen, Germany) (25 cases and 44 controls).

In brief, FDG (5 MBq $kg^{-1}$) was administered intravenously after an overnight fast, and imaging was performed 60 min later. After unenhanced CT for attenuation correction and anatomical co-registration, PET imaging was performed with 3 min per bed position in three-dimensional mode. Reconstruction of the attenuation-corrected images was done using an ordered subset expectation maximization algorithm with point-spread function (PSF) and time-of-flight (three iterations, 24 subsets, matrix size 192 × 192, 4-mm Gaussian postprocessing filter, voxel size 2 mm × 2 mm × 2 mm)(GE PET/CT). On the Siemens Biograph 64 PET/CT, we used visually comparable PSF reconstruction protocols (TrueX) (four iterations, 21 subsets, 3-mm Gaussian postprocessing filter, matrix size 336 × 336, voxel size 2 mm × 2 mm × 2 mm). These acquisition and reconstruction parameters adhere to international guidelines and have previously been described [14, 15].

By the time of diagnosis, routine evaluation of the PET images included assessment of aorta and its main branches but did not include TA and MA assessment. Segmental homogenous arterial FDG uptake above liver uptake in the aorta and/or supra-aortic limb branches was considered suggestive of large vessel vasculitis.

### 18F-FDG PET/CT visual assessment

To minimise risk of bias, PET images were evenly cropped to include only the head and neck (Fig. 1a). Scans were anonymised and assigned a random id number. Qualitative image analysis was made using Hermes (Hermes Medical Solutions, Stockholm, Sweden).

Images were assessed in random order by four nuclear medicine physicians who had no particular expertise in reporting 18F-FDG PET scans performed in patients with suspected inflammatory disease including vasculitis (AH, SK, KH and JE). Assessors had different levels of experience (6–12 years) and came from two different institutions. Assessors were blinded to clinical information and diagnosis. Before the assessment, a training set of five GCA 18F-FDG PET/CTs (not part of the GCA cohort) were reviewed side-by-side with an expert nuclear medicine physician (LG) with particular experience reporting 18F-FDG PET/CT in patients with inflammatory diseases, including GCA.

Temporal (TA), maxillary (MA) and vertebral (VA) arteries were visually scored bilaterally. Based on experience from, e.g., patients with head and neck cancers, we consider any 18F-FDG uptake in non-inflamed cranial arteries uncommon, and consequently, any arterial 18F-FDG uptake above surrounding tissue was considered indicative of inflammation. In the presence of cranial artery 18F-FDG uptake, the intensity was graded low or high (Fig. 1b). A consensus diagnosis for each segment assessed was obtained by majority conclusion. In the rare case of a given segment considered positive and negative by an equal number of readers, consensus was settled by the expert nuclear medicine physician (LG).

A vessel domain (TA, MA or VA) was considered positive if any of two bilateral assessments were positive. Evaluating diagnostic sensitivity of combinations of vascular domains, a scan was considered positive if any of the segments were positive, and considered negative if all segments evaluated were negative.

### Statistics

Data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at Aarhus University [16].

Student t test was used for quantitative data. Normality was checked using histograms and QQ-plots. Interreader agreement was evaluated by Fleiss kappa. Interpreting of Kappa values followed: ≤0 = poor, 0.01–0.20 = slight, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial, and 0.81–1.00 = almost perfect [17].

A significance level of 0.05 was considered significant. Statistical analysis was performed using Stata (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

## Results

### Participants

A total of 44 GCA patients were identified and matched with 44 controls. A patient flow diagram is shown in Fig. 2. None of the controls were excluded due to a history of PMR or GCA.

In both case and control group, the mean age was 69 years (mean age difference 0.1 years, $p = 0.45$) and 25 of 44 were women. Baseline characteristics of the GCA cases are shown in Table 1.

### Diagnostic accuracy of cranial 18F-FDG PET/CT

Cross tabulation of diagnosis and cranial artery FDG uptake for each reader and for final consensus assessment for each of the three vessel domains are shown in Table 2.

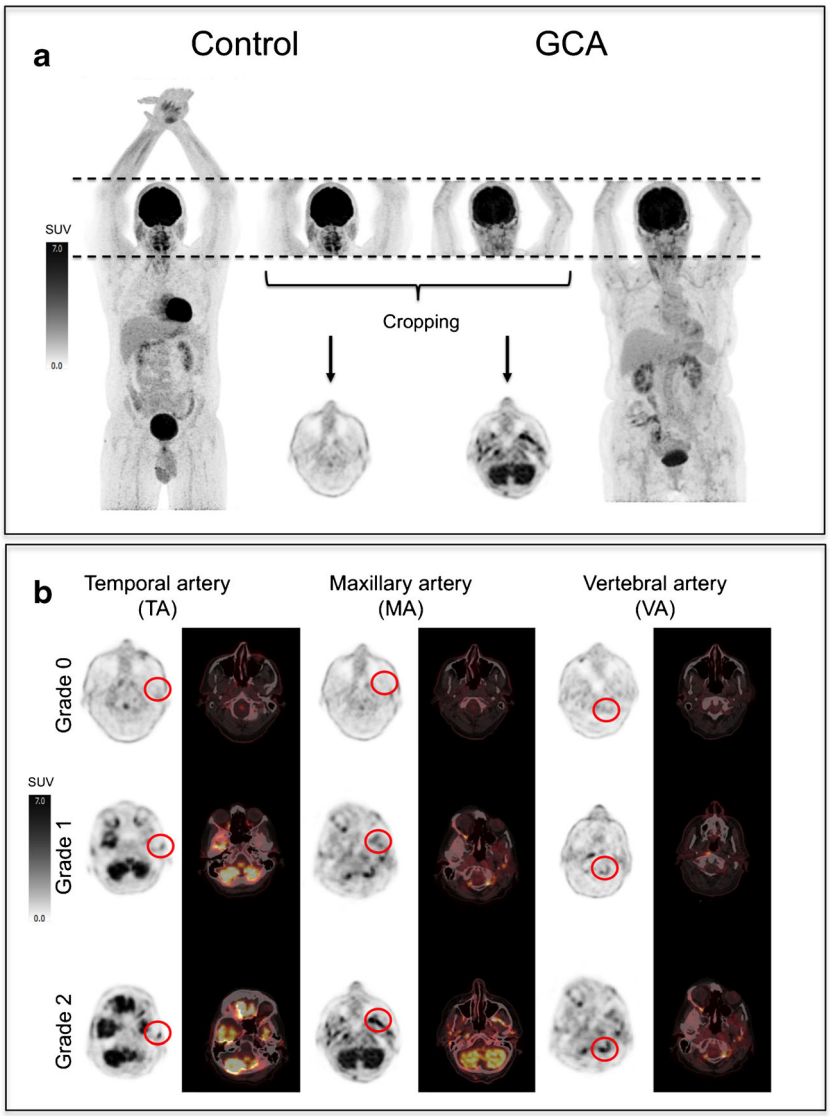


**Fig. 1** 18F-FDG PET/CT imaging assessment **a** To minimize risk of bias, conventional 18F-FDG PET/CT images were cropped to include only the head and neck in both GCA patients and controls. **b** 18F-FDG uptake in cranial arteries was scored as grade 0–2 with 0 representing uptake not above the surrounding tissue, 1 representing uptake just above the surrounding tissue, and grade 2 representing uptake significantly above the surrounding tissue

Overall diagnostic sensitivity and specificity (consensus) of cranial 18F-FDG PET/CT was 82 and 100%. Excluding the assessment of VA and evaluating only the assessment of TA and MA, a sensitivity of 64% and a specificity of 100% was obtained. Since specificity was high by simply assessing presence or absence of FDG uptake in cranial arteries, a grading of FDG uptake in low or high intensity did not improve diagnostic accuracy. Fig. 3 provides typical examples of FDG uptake in cranial arteries of GCA patients.

Interreader agreement was 91% and Fleiss kappa 0.82 for the PET diagnosis based on the cranial arteries. In a per segment analysis of the graded PET scores, agreement was 93% and Fleiss kappa 0.82.

Among the 44 GCA patients, 34 patients had PET verified large vessel involvement. Twenty-nine of the 34 LV-GCA patients were also cranial artery PET positive. Seven GCA patients only showed cranial artery FDG uptake without large vessel involvement and three GCA patients were completely PET negative.

Table 3 provides cross tabulation of TAB result and the consensus cranial artery PET assessment. In the patients in whom TAB was performed, 89% were TAB positive and 89% cranial PET positive. Although sensitivity of cranial 18F-FDG PET/CT equaled the sensitivity of TAB, there were GCA cases where only one of the diagnostic tests was positive. Evaluating exclusively 18F-FDG uptake in TA, PET/CT revealed inflammation in half of the TAB positive GCA patients.

In contrast to the TA and MA, the VA was visually assessed at the time of the initial PET/CT report. In 38/44 GCA cases, baseline and retrospective vertebral PET diagnosis was in agreement. In five cases baseline assessment of VA was negative whereas retrospective scoring was positive and in one case retrospective scoring was negative and baseline scoring positive.

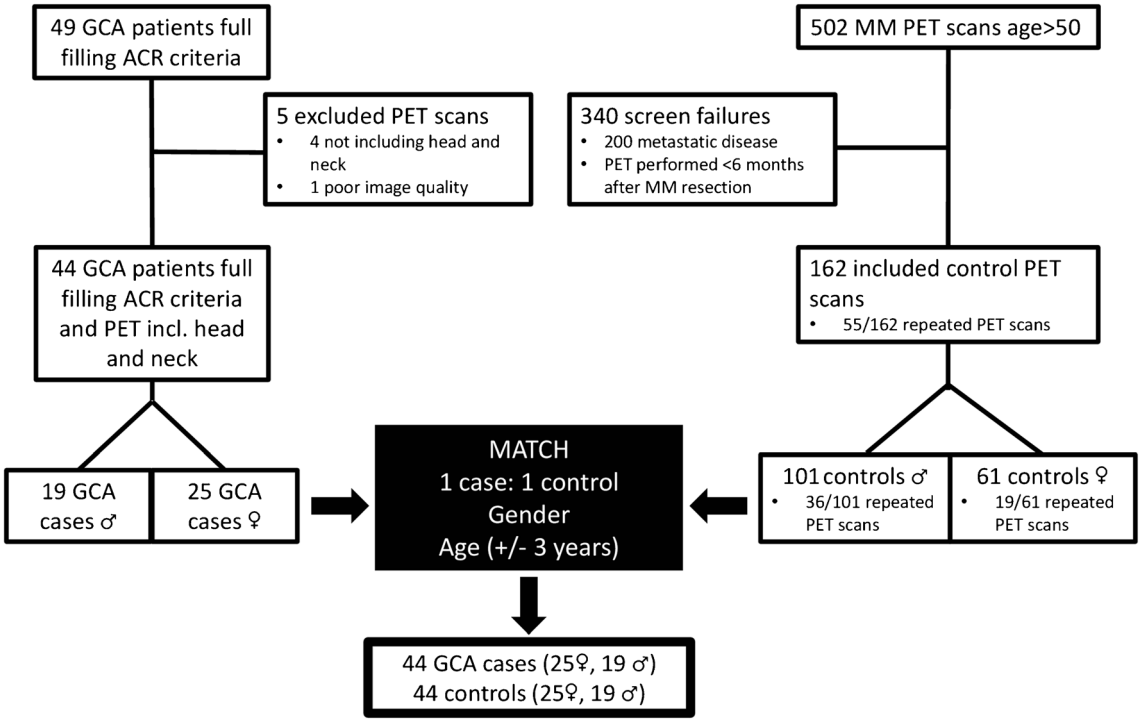


**Fig. 2** Patient flow diagram. The flow diagram shows the number of GCA patients and the number of controls that were excluded. Subsequently, each GCA patient was matched on gender and age (± 3 years) with a control patient, obtaining 44 cases and 44 controls. GCA, giant cell arteritis; ACR, American College of Rheumatology; MM, malignant melanoma

None of the diagnostic procedures performed caused any complications or immediate side effects. The results of this retrospective analysis did not in any case change diagnosis or treatment of the participants.

## Discussion

This is the first study to show that simple visual assessment of cranial artery inflammation by conventional 18F-FDG PET/CT can accurately diagnose cranial GCA in glucocorticoid-naïve patients with a sensitivity between 64 and 82%, depending on ex- or inclusion of vertebral arteries, and a specificity of 100%. There was an almost perfect interreader agreement among assessors with different levels of experience. Therefore, cranial PET/CT provides a diagnostic tool as sensitive as the TAB and a specificity and interreader agreement hard to match by any other diagnostic tools.

Inflammation of the cranial arteries, especially the smaller TA and MA, is usually considered non-detectable by 18F-FDG PET/CT [5]. In an early PET study of temporal artery US positive GCA patients fulfilling the 1990 ACR criteria, Brodmann et al. concluded that inflamed TAs were not detectable by PET systems of that time [18]. Diameter of the cranial vessels and proximity to the skin-air interface and to the brain has been argued to hamper sufficient PET imaging of cranial arteries. Most studies of diagnostic accuracy of 18F-FDG PET/CT in GCA have, therefore, considered only large vessel involvement [19–22]. Nevertheless, FDG uptake in MA was recently reported in 12 of 41 patients suspected of GCA, and has also been reported in TA and occipital arteries of GCA patients [10–12]. Improved resolution of newer PET systems in combination with relatively detailed low-dose CT allows for more accurate anatomical co-localisation of morphology and metabolism. Taken together, this may to some extent explain why today's conventional 18F-FDG PET/CT can accurately diagnose cranial GCA.

The strengths of this study are several. Firstly, GCA patients were treatment-naïve and represented a variety of phenotypical GCA cases. Secondly, the nuclear medicine physicians were blinded to patients' diagnosis and PET images had been cropped to avoid risk of bias from visualisation of large vessel involvement. Thirdly, although only a brief training session was given, the multiple readers assessing PET images obtained an almost perfect agreement.

The results of this study are highly generalizable. A conventional 18F-FDG PET/CT protocol was followed and the evaluation of the images was a simple assessment of the presence or absence of FDG uptake in the cranial arteries. The nuclear medicine physicians who assessed the images in this case-control study had various levels of experience and came from two different centers. None of them had experience with this specific assessment, and they were only trained for half an hour by a nuclear medicine physician with particular

**Table 1** Baseline characteristics of GCA patients

| | |
|---|---|
| Total number of patients | 44 |
| Demographics | |
| Female gender | 25 (57%) |
| Age, years [mean (SD)] | 69 (7) |
| Clinical characteristics | |
| Cranial symptoms[a] | 38 (86%) |
| Headache or scalp tenderness | 35 (80%) |
| Jaw claudication | 12 (27%) |
| Visual disturbances | 9 (20%) |
| Permanent loss of vision | 0 |
| Amaurosis fugax | 3 (7%) |
| Double vision | 0 |
| Blurred vision | 6 (14%) |
| Extremity claudication | 8 (18%) |
| Constitutional symptoms[b] | 35 (80%) |
| Patients global NRS [median (IQR)] | 8 (5–10) |
| CRP, mg/L [median (95% CI)] | 70 (58–85) |
| Diagnostic tests | |
| ACR criteria full-filled (by design) | 44 (100%) |
| Days from 18F-FDG PET/CT to treatment initiation [median (range)] | 1 (0–10) |
| TAB performed[c] | 41 (93%) |
| TAB positive | 35 (80%) |
| Number of days treated before TAB [median (range)] | 6 (−8–12) |
| Number of days from PET/CT to TAB [median (range)] | 7 (−8–20) |
| 18F-FDG PET verified LV involvement | 34 (77%) |

If not otherwise specified, data are numbers and percentages (%) of patients. [a] Headache, scalp tenderness, jaw claudication and/or visual disturbances, [b] fever ≥38°C, weight loss ≥5 kg and/or profound night sweats, [c] TAB procedure failed in three patients (2 biopsies included only venous vessel, 1 procedure cancelled), [e] PET verified large vessel involvement defined as homogenous FDG uptake in aorta and/or supra-aortic limb branches

SD, standard deviation; NRS numerical rang scale; IQR, interquartile range; CRP, c-reactive protein; ACR, 1990 American College of Rheumatology criteria for GCA; TAB, temporal artery biopsy; 18F-FDG PET/CT, Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography; LV, large vessel

experience with 18F-FDG PET/CT in patients with inflammatory diseases including GCA. Still, an almost perfect interreader agreement was obtained.

Several limitations to the study need mentioning. Firstly, it was retrospective in design and the selected control group was age and sex-matched earlier MM diagnosed patients rather than patients with a suspected diagnosis of GCA. However, the risk of misclassification of GCA suspected patients, e.g., PMR patients with subclinical GCA, was considered significant in this retrospective study design. Further prospective studies with a control group of patients with suspected, but finally excluded GCA, are needed to confirm our results. Secondly, most institutions do not have day- to-day access to 18F-FDG PET/CT and examinations are therefore often performed in corticosteroid treated patients. Performing serial PET/CT in new-onset LV-GCA patients, we recently showed a sustained level of sensitivity after 3 days of treatment whereas 10 days of treatment significantly reduced 18F-FDG PET/CT sensitivity in the large arteries [14]. Whether this is also the case in smaller cranial arteries will need to be determined in further studies.

Thirdly, none of the patients included presented with loss of vision, the most feared GCA complication. However, we expect that GCA patients presenting with symptoms indicating manifest inflammation of cranial arteries would also be more likely to show cranial artery 18F-FDG uptake. Moreover, the GCA cohort did include patients revealing other ischaemic symptoms such as jaw claudication and visual disturbances (Table 1). Therefore, we do not consider it likely that this minor selection bias negatively affects the true sensitivity of the PET scan.

Fourthly, TAB performed prior to the PET scan potentially increases metabolism in the area of the biopsy and may, therefore, cause false positive signs of inflammation. In two cases, GCA patients had TAB done before the PET scan. In these cases, the temporal artery was considered PET positive. However, in both patients the cranial PET also revealed increased 18F-FDG uptake in other cranial arteries than at the

**Table 2** Cross tabulation of clinical diagnosis and the assessment of FDG uptake by four readers and their consensus diagnosis

| | | Reader 1 | | Reader 2 | | Reader 3 | | Reader 4 | | Consensus | | Accuracy | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Reference diagnosis | | | | | | | | | | | |
| | | GCA | control | GCA | control | GCA | control | GCA | control | GCA | control | sens | spec |
| PET diagnosis in different vascular domains | TA/MA/VA | | | | | | | | | | | | |
| | Positive | 38 | 2 | 35 | 0 | 34 | 3 | 33 | 2 | **36** | **0** | **82% (67–92%)** | **100% (92–100%)** |
| | Negative | 6 | 42 | 9 | 44 | 10 | 41 | 11 | 42 | **8** | **44** | | |
| | TA/MA | | | | | | | | | | | | |
| | Positive | 30 | 1 | 27 | 0 | 26 | 0 | 27 | 2 | **28** | **0** | **64% (48–78%)** | **100% (92–100%)** |
| | Negative | 14 | 43 | 17 | 44 | 18 | 44 | 17 | 42 | **16** | **44** | | |
| | TA | | | | | | | | | | | | |
| | Positive | 19 | 1 | 18 | 0 | 16 | 0 | 19 | 0 | **16** | **0** | **36%** | **100%** |
| | Negative | 25 | 43 | 26 | 44 | 27 | 44 | 24 | 44 | **28** | **44** | **(22–52%)** | **(92–100%)** |
| | MA | | | | | | | | | | | | |
| | Positive | 28 | 0 | 28 | 0 | 24 | 0 | 25 | 2 | **27** | **0** | **61%** | **100%** |
| | Negative | 16 | 44 | 18 | 44 | 19 | 44 | 18 | 42 | **17** | **44** | **(46–76%)** | **(92–100%)** |
| | VA | | | | | | | | | | | | |
| | Positive | 34 | 1 | 34 | 0 | 34 | 3 | 33 | 1 | **35** | **0** | **80%** | **100%** |
| | Negative | 10 | 43 | 10 | 44 | 10 | 41 | 11 | 43 | **9** | **44** | **(65–90%)** | **(92–100%)** |

Results of the assessment of single vessel domains as well as the assessment of combination of domains are given. Sensitivity and specificity of the consensus diagnosis are specified. Corresponding sensitivity and specificity for the assessment of TA/MA/VA by the four individual readers ranged between 70 and 86% and 93–100%, respectively. For the four readers' individual assessment of only VA/TA sensitivity ranged 59–68% and specificity 95–100%. If not otherwise specified, numbers are numbers of patients. Brackets contain 95% confidence intervals. Sens, sensitivity; spec, specificity; TA, temporal artery; MA, maxillary artery, VA, vertebral artery

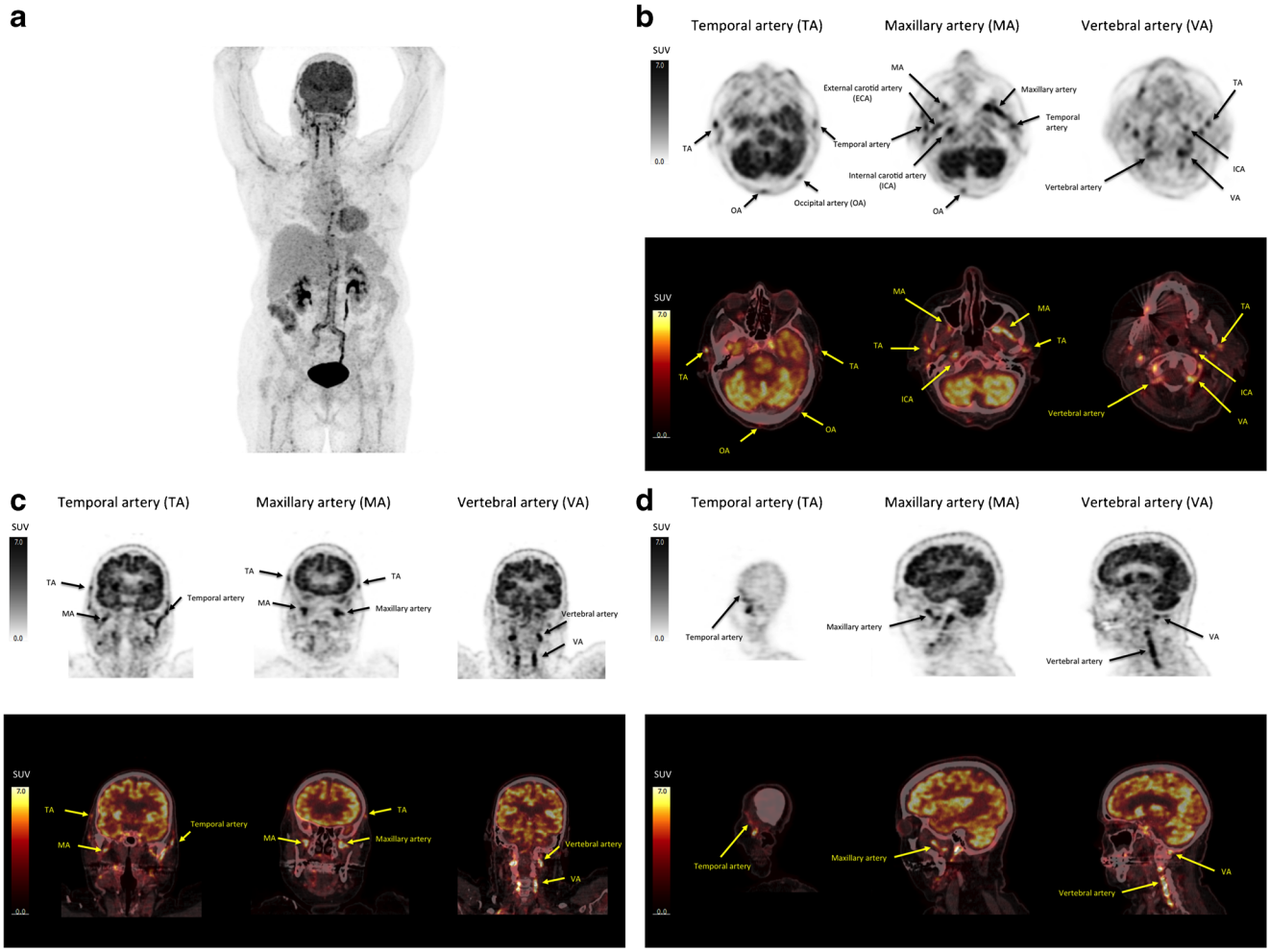


**Fig. 3** Examples of FDG uptake in cranial arteries of GCA patients **a** Maximum Intensity Projection (MIP) image of a GCA patient with involvement of both cranial and large vessels. **b**, **c**, **d** Transaxial, coronal and sagittal representations of the most common areas of 18F-FDG focality in the cranial arteries of the GCA patient. Upper panels, PET images; lower panels, concordant PET/CT fusion images

**Table 3** FDG uptake in GCA patients with positive and negative temporal artery biopsies

| | | Temporal artery biopsy | | |
|---|---|---|---|---|
| | | positive | negative | PET sensitivity with TAB as reference |
| PET diagnosis in different vascular domains | TA | | | |
| | PET positive | 18 | 0 | 51% (34–69%) |
| | PET negative | 17 | 6 | |
| | TA/MA | | | |
| | PET positive | 24 | 3 | 69% (51–83%) |
| | PET negative | 11 | 3 | |
| | TA/MA/VA | | | |
| | PET positive | 31 | 4 | 89% (73–97%) |
| | PET negative | 4 | 2 | |

Cross tabulation of the assessment of FDG uptake and result of temporal artery biopsy in 41 GCA patients (TAB result not available in remaining three GCA patients)

Results of the assessment of single vessel domains as well as the assessment of combination of domains are given. TA, temporal artery; MA, maxillary artery, VA, vertebral artery

site of the biopsy. We therefore find it unlikely that the TAB influenced the overall accuracy of the results.

Previous imaging studies of cranial artery inflammation in GCA patients have documented involvement of other cranial arteries such as the occipital, facial and external carotid arteries [23–27]. Although we do occasionally find FDG uptake in these arteries (as also depicted in Fig. 3), inflammation in these segments was not systematically addressed in our study. It is likely that the inclusion of additional cranial arteries in the assessment potentially would result in increased sensitivity of the PET scan. However, we aimed to evaluate a simple assessment of cranial artery inflammation that would not require extraordinary training.

The EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice suggests that imaging is performed in all patients suspected of GCA and that the imaging of choice is based on the patients' phenotypic presentation and the availability of the imaging test. The need for reliable diagnostic tests is further necessitated by the emergence of clinical trials of targeted synthetic and biologic DMARDs in GCA to justify the costs of approved potent, yet expensive, treatment regimens for GCA patients [28–30].

The results of this study implicate, that in all patients ≥50 years of age, in whom a PET-scan is performed, either at the suspicion of GCA or even in patients with inflammation or fever of unknown origin in whom GCA is frequently diagnosed [31–33], the PET examination should include head and neck, and the cranial arteries should be evaluated for 18F-FDG uptake by the reading physician. The excellent reliability and specificity of cranial FDG uptake implicates that in a patient with a clinical suspicion of GCA, this finding makes further diagnostic tests, such as a TAB, redundant.

**Acknowledgements** This work was funded by The Danish Rheumatism Association, Aarhus University, Aarhus University Hospital, Brødrene Hartmann Fond, A.P. Moeller Foundation, and Aase & Ejnar Danielsen Foundation.

We would like to thank Irene Dalsgaard Nielsen, medical secretary, Department of Plastic and Breast surgery, Aarhus University Hospital for assisting the assessment of eligibility of the controls and Anne-Birgitte Blavnsfeldt, MD, Department of Rheumatology, Aarhus University Hospital for editing the manuscript.

**Funding** This study was funded by The Danish Rheumatism Association, Aarhus University, Aarhus University Hospital, Brødrene Hartmann Foundation, A.P. Moeller Foundation, Aase & Ejnar Danielsen Foundation.

## Compliance with ethical standards

**Ethical approval** All procedures performed in the study were in accordance with the ethical standards of the National Committee on Health Research Ethics and with the 1964 Helsinki Declaration and its later amendments.

The Central Denmark Region Committees on Health Research Ethics (reference number 1–10–72-246-16 and 1–10–72-60-14) and The Danish Data Protection Agency (reference number 1–16–02-380-14 and 1–16–02-481-16) approved the study.

**Informed consent** Ethical approval was given to assess 18F-FDG PET/CT of controls and to check prior and current diagnoses in their electronic medical record without informed consent from the patient. All GCA patients gave written, informed consent.

**Conflicts of interests** Berit Dalsgaard Nielsen has received fees for speaking from Roche. Ellen-Margrethe Hauge has received fees for speaking from MSD, AbbVie, UCB and Sobi; and received research funding to Aarhus University Hospital from Roche and Novartis. Kresten Krarup Keller has received fees for speaking from Pfizer.

**Disclaimers** The views expressed in the submitted article are the authors' own and not an official position of the institution or funder.

## References

1. Ashton-Key MR, Gallagher PJ. False-negative temporal artery biopsy. Am J Surg Pathol. 1992;16:634.
2. Luqmani R, Lee E, Singh S, Gillett M, Schmidt WA, Bradburn M, et al. The role of ultrasound compared to biopsy of temporal arteries in the diagnosis and treatment of giant cell arteritis (TABUL): a diagnostic accuracy and cost-effectiveness study. Health Technol Assess (Rockv). 2016;20:1–270.
3. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2009;68:318–23.
4. Bowling K, Rait J, Atkinson J, Srinivas G. Temporal artery biopsy in the diagnosis of giant cell arteritis: does the end justify the means? Ann Med Surg. 2017;20:1–5.
5. Dejaco C, Ramiro S, Duftner C, Besson FL, Bley TA, Blockmans D, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis. 2018;77(5):636–43.
6. Treglia G, Mattoli MV, Leccisotti L, Ferraccioli G, Giordano A. Usefulness of whole-body fluorine-18-fluorodeoxyglucose positron emission tomography in patients with large-vessel vasculitis: a systematic review. Clin Rheumatol. 2011;30:1265–75.
7. Besson FL, Parienti J-J, Bienvenu B, Prior JO, Costo S, Bouvard G, et al. Diagnostic performance of 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2011;38:1764–72.
8. Soussan M, Nicolas P, Schramm C, Katsahian S, Pop G, Fain O, et al. Management of large-vessel vasculitis with FDG-PET. Medicine (Baltimore). 2015;94:e622.
9. Grayson PC, Alehashemi S, Bagheri AA, Civelek AC, Cupps TR, Kaplan MJ, et al. 18 F-Fluorodeoxyglucose-positron emission tomography as an imaging biomarker in a prospective, longitudinal cohort of patients with large vessel vasculitis. Arthritis Rheumatol. 2018;70:439–49.
10. Sammel AM, Hsiao E, Nguyen K, Schembri G, Laurent R. Maxillary artery 18F-FDG uptake as a new finding on PET/CT scan in a cohort of 41 patients suspected of having giant cell arteritis. Int J Rheum Dis. 2018;21:560–2.
11. Rehak Z, Szturz P, Kren L, Fojtik Z, Stanicek J. Upsampling from aorta and aortic branches: PET/CT hybrid imaging identified 18F-FDG hypermetabolism in inflamed temporal and occipital arteries. Clin Nucl Med. 2014;39:e84–6.
12. Maestri Brittain J, Gormsen L, von Benzon E, Andersen K. Concomitant polymyalgia rheumatica and large-vessel vasculitis visualized on 18F-FDG PET/CT. Diagnostics. 2018;8:27.

13. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American college of rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990;33:1122–8.
14. Nielsen BD, Gormsen LC, Hansen IT, Keller KK, Therkildsen P, Hauge E-M. Three days of high-dose glucocorticoid treatment attenuates large-vessel 18F-FDG uptake in large-vessel giant cell arteritis but with a limited impact on diagnostic accuracy. Eur J Nucl Med Mol Imaging. 2018;45:1119–28.
15. Boellaard R, Delgado-Bolton R, Oyen WJG, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2015;42:328–54.
16. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377–81.
17. Sim J, Wright CC. The kappa statistic in reliability studies: use, interpretation, and sample size requirements. Phys Ther. 2005;85:257–68.
18. Brodmann M, Lipp RW, Passath A, Seinost G, Pabst E, Pilger E. The role of 2-18F-fluoro-2-deoxy-D-glucose positron emission tomography in the diagnosis of giant cell arteritis of the temporal arteries. Rheumatology. 2004;43:241–2.
19. Prieto-González S, Depetris M, García-Martínez A, Espígol-Frigolé G, Tavera-Bahillo I, Corbera-Bellata M, et al. Positron emission tomography assessment of large vessel inflammation in patients with newly diagnosed, biopsy-proven giant cell arteritis: a prospective, case–control study. Ann Rheum Dis. 2014;73:1388–92.
20. Förster S, Tato F, Weiss M, Czihal M, Rominger A, Bartenstein P, et al. Patterns of extracranial involvement in newly diagnosed giant cell arteritis assessed by physical examination, colour coded duplex sonography and FDG-PET. Vasa. 2011;40:219–27.
21. Lehmann P, Buchtala S, Achajew N, Haerle P, Ehrenstein B, Lighvani H, et al. 18F-FDG PET as a diagnostic procedure in large vessel vasculitis-a controlled, blinded re-examination of routine PET scans. Clin Rheumatol. 2011;30:37–42.
22. Henes JC, Müller M, Krieger J, Balletshofer B, Pfannenberg AC, Kanz L, et al. [18F] FDG-PET/CT as a new and sensitive imaging method for the diagnosis of large vessel vasculitis. Clin Exp Rheumatol. 2008;26:S47–52.
23. Pfadenhauer K, Weber H. Duplex sonography of the temporal and occipital artery in the diagnosis of temporal arteritis. A prospective study. J Rheumatol. 2003;30:2177–81.
24. Klink T, Geiger J, Both M, Ness T, Heinzelmann S, Reinhard M, et al. Giant cell arteritis: diagnostic accuracy of MR imaging of superficial cranial arteries in initial diagnosis—results from a multicenter trial. Radiology. 2014;273:844–52.
25. Rhéaume M, Rebello R, Pagnoux C, Carette S, Clements-Baker M, Cohen-Hallaleh V, et al. High-resolution magnetic resonance imaging of scalp arteries for the diagnosis of giant cell arteritis: results of a prospective cohort study. Arthritis Rheumatol. 2017;69:161–8.
26. Schmidt WA, Natusch A, Möller DE, Vorpahl K, Gromnica-Ihle E. Involvement of peripheral arteries in giant cell arteritis: a color Doppler sonography study. Clin Exp Rheumatol. 2002;20:309–18.
27. Ješe R, Rotar Ž, Tomšič M, Hočevar A. The role of colour doppler ultrasonography of facial and occipital arteries in patients with giant cell arteritis: a prospective study. Eur J Radiol. 2017;95:9–12.
28. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of tocilizumab in giant-cell arteritis. N Engl J Med. 2017;377:317–28.
29. Langford CA, Cuthbertson D, Ytterberg SR, Khalidi N, Monach PA, Carette S, et al. A randomized, double-blind trial of abatacept (CTLA-4Ig) for the treatment of giant cell arteritis. Arthritis Rheumatol. 2017;69:837–45.
30. Dejaco C, Brouwer E, Mason JC, Buttgereit F, Matteson EL, Dasgupta B. Giant cell arteritis and polymyalgia rheumatica: current challenges and opportunities. Nat Rev Rheumatol. 2017;13:1–15.
31. Meller J, Sahlmann CO, Gürocak O, Liersch T, Meller B. FDG-PET in patients with fever of unknown origin: the importance of diagnosing large vessel vasculitis. Q J Nucl Med Mol Imaging. 2009;53:51–63.
32. Muto G, Yamashita H, Takahashi Y, Miyata Y, Morooka M, Minamimoto R, et al. Large vessel vasculitis in elderly patients: early diagnosis and steroid-response evaluation with FDG-PET/CT and contrast-enhanced CT. Rheumatol Int. 2014;34:1545–54.
33. Fuchs M, Briel M, Daikeler T, Walker UA, Rasch H, Berg S, et al. The impact of 18F-FDG PET on the management of patients with suspected large vessel vasculitis. Eur J Nucl Med Mol Imaging. 2012;39:344–53.