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Visual and semiquantitative assessment of cranial artery inflammation with FDG-PET/CT in giant cell arteritis

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ABSTRACT

Background and aim: Assessing cranial artery inflammation plays an important role in the diagnosis of cranial giant cell arteritis (C-GCA). However, current diagnostic tests are limited. The use of fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT imaging is an established tool for assessing large vessel inflammation but is currently not used for assessment of the cranial arteries. This study aimed to evaluate the accuracy of FDG-PET/CT in the diagnosis of biopsy proven C-GCA and its relation to clinical presentation.
Methods: This retrospective case control study included temporal artery biopsy (TAB) positive C-GCA patients and age- and sex-matched controls. FDG-PET/CT scans were performed according to EANM/EARL guidelines, visually assessed by an experienced nuclear medicine physician, and semiquantitatively assessed using the maximum standardised uptake value (SUVmax). The visual and semiquantitative assessments were performed on the temporal arteries, maxillary arteries, vertebral arteries, and occipital arteries. Clinical signs and symptoms were scored for comparison.
Results: A total of 24 C-GCA patients and 24 controls were included in the study. Visual analysis revealed an 83% sensitivity and a 75% specificity. Receiver operating characteristic (ROC) analysis of the semiquantitative assessment revealed a 79% sensitivity and a 92% specificity when measuring SUVmax in the cranial arteries. Visual and semiquantitative assessments showed moderate agreement (Fleiss kappa 0.55). There was a positive correlation between the number of cranial symptoms and the SUVmax in the vertebral artery.
Conclusion: FDG-PET/CT can reliably diagnose C-GCA by assessing cranial artery inflammation using SUVmax. Extending the use of FDG-PET/CT to include assessment of the cranial arteries may improve its diagnostic value in GCA and provide a suitable alternative to TAB. Moderate agreement between visual and semiquantitative assessment methods suggest diagnostic accuracy may be improved by further standardisation.

Introduction

Giant cell arteritis (GCA) is a large vessel vasculitis most commonly affecting the aorta and its major branches. Within the GCA spectrum, different patterns of vessel involvement may be recognised [1]. In cranial GCA (C-GCA), the arteries of the head and the neck, such as the temporal, maxillary, and vertebral arteries are affected. In large vessel GCA (LV-GCA), arteries such as the aorta and subclavian arteries may be involved. Approximately 70% of patients present with an overlap of these two disease patterns. Nonetheless, C-GCA and LV-GCA differ in their clinical presentation, complications, diagnostic approach, and may also have a different outcome [2].

The clinical presentation of C-GCA includes new-onset headache often characterized by a burning sensation on the scalp, jaw claudication and an enlarged painful temporal artery upon palpation. Importantly, visual manifestations due to ischaemia of the optic nerve are common in C-GCA [3]. These manifestations may be intermittent at the outset but can lead to irreversible vision loss if left untreated [4]. Other medical emergencies associated with C-GCA are transient ischaemic attacks (TIA) and cerebrovascular accidents (CVA). The clinical presentation of LV-GCA includes claudication of the extremities, discrepancy in blood

Abbreviations: CRP, C-reactive protein; FDG-PET, fluorine-18-fluorodeoxyglucose positron-emission tomography; CT, computed tomography; GCA, giant cell arteritis; TAB, temporal artery biopsy; US, ultrasound; SUV, standardised uptake value; VOI, volume of interest; SCV, superior caval vein; TBR, target-to-background ratio

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pressure of the upper extremities, and an abnormal radial pulse. Constitutional symptoms such as fever, malaise, and weight loss present equally in both disease variants [5].

The risk of ischaemic complications stresses the need for fast diagnosis of C-GCA [3]. Temporal artery biopsy (TAB) has long been considered as the gold standard for diagnosing GCA. Because of its high specificity, TAB can confirm a C-GCA diagnosis with a high level of certainty. However, TAB has a low sensitivity and a high interobserver variability between pathologists has been reported [6]. Additionally, treatment is often started before the TAB results are available and is also rarely altered after a negative TAB result [7].

The European League Against Rheumatism (EULAR) recommends that after careful clinical examination, imaging is the preferred first diagnostic test [8]. Duplex ultrasonography (US) of the axillary and temporal arteries has a 54% sensitivity and an 81% specificity, and highly depends on the skill of the examiner and the US machine [6]. Magnetic resonance imaging (MRI) can also be used in C-GCA by assessing the temporal and occipital arteries, resulting in a sensitivity of 93% and a specificity of 88% [9]. Limiting factors of MRI are long waiting times and its unknown use in LV-GCA.

Fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT is an imaging test routinely used in GCA patients to detect large artery involvement. Due to their high metabolic activity, inflammatory cells such as macrophages and lymphocytes show high uptake of FDG [10]. The recommended way of analysing FDG uptake in the arteries is by visual assessment. Additionally, semiquantitative measurements of FDG uptake, such as the standardised uptake value (SUV), are regularly used in research and may offer a more objective measure of inflammation [11].

The recommended use of FDG-PET/CT in GCA is currently limited to detect extracranial vascular involvement. Its use in the diagnosis of C-GCA is currently not recommended, but the potential application of FDG-PET/CT in C-GCA should be evaluated [8,11]. Assessment of the cranial arteries has historically been difficult due to the high physiological FDG uptake in the brain. In 2004, a study deemed FDG-PET unsuitable to detect GCA in arteries with a diameter smaller than 4 mm, therefore excluding most cranial arteries [12].

Using newer generation PET/CT scanners and new reconstruction methods, recent studies show high diagnostic accuracy when using FDG-PET/CT for detecting cranial artery involvement in GCA [13,14]. These studies however included only visual assessment of cranial artery inflammation, which is prone to subjectivity. Additionally, no study yet investigated the link between the clinical signs of cranial artery inflammation and FDG uptake in the cranial arteries.

The current study aimed to evaluate the diagnostic accuracy of FDG-PET/CT in TAB positive C-GCA patients, using both visual and semiquantitative methods. Additionally, results of the assessments were compared with the clinical presentation of the patient.

Methods

This retrospective case-control study was performed at the departments of Rheumatology and Clinical Immunology and Nuclear Medicine and Molecular Imaging of the University Medical Center Groningen (UMCG), the Netherlands. Data were collected from the hospital's pathology database, health record system, and radiology servers. The study was approved by the Medical Ethics Review Board (METc) of the UMCG (METc number 2018/472).

Cases

Reports of TABs performed between 2008 and 2018 were obtained from the pathology database. Positive TABs were selected and the hospital health record system was subsequently checked for FDG-PET/CT scans. Demographic data, signs and symptoms, and relevant medical history were also retrieved from the health record system.

Patients were excluded if they were concurrently diagnosed with malignancies or autoimmune diseases. Glucocorticoid therapy notably decreases the FDG-PET/CT signal 3 days after commencing therapy [15]. Therefore, patients receiving glucocorticoid therapy were excluded if the treatment duration exceeded 3 days at the time of FDG-PET/CT.

Controls

Follow up scans of patients diagnosed with melanoma without evidence of disease on FDG-PET/CT were chosen as controls. Scans were performed between 2013 and 2018. Patients treated for a melanoma at time of imaging were excluded. Additionally, patients who underwent surgery in the six months prior to the FDG-PET/CT scan were excluded. Patients diagnosed with other malignancies or autoinflammatory diseases were also excluded. Controls were matched for age ($\pm$ 3 years) and sex (1:1).

Assessment of clinical presentation

Signs and symptoms from physician reports closest before the date of FDG-PET/CT were collected from the electronic health record system. The data collected on cranial symptoms were the presence of new or different headache, scalp tenderness, temporal artery tenderness, ischaemia-related vision loss, jaw claudication, and the occurrence of a transient ischaemic attack (TIA) or a cerebrovascular accident (CVA). The data collected on the systemic symptoms were the presence of fever, weight loss, malaise, night sweats, arm claudication, and leg claudication.

FDG-PET/CT scanning procedure

All FDG-PET/CT scans of GCA patient cases and melanoma patient controls were performed on a Biograph mCT camera system (Siemens Medical Systems, Knoxville, TN). Patients were instructed to fast 6 hours prior to intravenous injection of 3 MBq/kg of FDG. Imaging commenced 60 minutes after injection and scanned either from head to proximal femur or from head to feet. The number of minutes per bed position was adjusted to the body weight of the patient. Since 2017, patients suspected of vasculitis had their head scanned for 5 minutes per bed position, which in our study concerns 7 out of 24 cases. Consequently, this constitutes a minor difference in scanning procedures between cases and controls in this study.

The PET image reconstruction method was selected by optimising reconstruction settings in order to best visualise the cranial arteries. Using iterative reconstruction, optimisation was performed by applying variable number of iterations and types of postreconstruction filters. PET reconstruction optimisation was based on expertise of a clinical physicist and chosen by an experienced nuclear medicine physician. The resulting PET reconstruction parameters comprised 4 iterations and 21 subsets. Reconstruction did not involve postreconstruction filtering, hereby deviating from standard protocols [16]. Additionally, reconstruction employed point-spread function (PSF), time of flight (TOF), and a matrix size of 512 $\times$ 512. Attenuation correction was also used. Imaging artefacts produced by (dental) prostheses as a result of attenuation correction were occasionally present but did not interfere when assessing the cranial arteries.

FDG-PET/CT assessment

Both visual assessment and semiquantitative assessments were performed using Syngo.Via software (version VB20A_HF05) (Siemens Healthcare, Erlangen, Germany). The temporal arteries (TA), maxillary arteries (MA), vertebral arteries (VA), and occipital arteries (OA) were scored bilaterally. All scans were anonymised and scored blinded for any clinical data.

Visual assessment

Visual assessment was performed by an experienced nuclear medicine physician. As described in a previous study, visual assessment was rated on a 0-2 scale [13]. Uptake was scored as '0' when there is no visible uptake higher than surrounding tissue, scored '1' when uptake is slightly higher than surrounding tissue, and scored '2' when uptake is significantly higher than surrounding tissue.

Semiquantitative assessment

Semiquantitative scoring was performed by measuring SUV within a volume of interest (VOI). Using the 3D-isocontour tools, spherical VOIs were drawn around the anatomical locations of the relevant cranial arteries. The SUVmax in every mentioned cranial artery of each case was recorded. Additionally, the highest measured SUVmax in the lumen of the superior caval vein (SCV) was also included as background blood pool activity, in order to calculate a target-to background ratio (TBR) to correct for possible variance in systemic uptake between patients [11].

Statistical analysis

Fisher's exact test was used to assess differences in visual assessment and quantitative assessment cross-tabulations. Fisher's exact test was also used to compare between the cranial artery assessment with the categorised clinical data. Mann-Whitney-U test was performed to test the differences between two groups of the quantitative assessment data, and the Kruskall-Wallis test was used to compare multiple groups. Receiver operating characteristics (ROC) analysis was used to determine the diagnostic value and to diagnostic cut-off values of the quantitative assessment. The area under the curve (AUC) of the ROC curve was used to compare between subgroups. Cohen's kappa (κ) was used to assess agreement between the visual and quantitative assessment methods, where a $\kappa<0$ was considered poor agreement, κ=0-0.20 fair agreement, κ=0.41-0.60 moderate agreement, κ=0.61-0.80 substantial agreement, and $\kappa>0.81$ almost perfect agreement, based on the Fleiss criteria (Fleiss DL, Statistical methods for rates and proportions. 2nd ed New York: 1981:212-236.). To calculate the correlations of the quantitative assessment and scored clinical presentation, Spearman's correlation coefficient was used. P-values less than 0.05 are considered statistically significant. All statistical analyses and graphs were made using GraphPad Prism software (version 8.0, GraphPad Software, Inc., CA).

Results

In total, 24 TAB positive C-GCA patients and 24 matched disease-free melanoma controls were included in the study. Baseline characteristics of the C-GCA patients are shown in Table 1. The median serum glucose level in the control group was 5.3 mmol/L (IQR 5.0-5.6) compared to 6.1 mmol/L (IQR 5.7-6.8) in the C-GCA group (p<0,001).

Overall, the intensity and distribution of FDG uptake in the cranial arteries differed between GCA patients and controls. High intensity uptake on visual assessment (visual score ≥ 1, see Fig. 1) and high SUVmax were found predominantly in C-GCA patients. The highest SUVmax across all arterial regions are plotted in Fig. 2. High intensity FDG uptake in C-GCA patients was predominantly found in the TA, MA, and VA. In the control group, SUVmax did not differ between left sided and right sided arteries. In the C-GCA group, highest and lowest median SUVmax values were observed in respectively the VA and OA. The mean SUVmax value of the SCV was comparable in the C-GCA and control groups.

Performance of visual assessment of cranial artery inflammation

Visually scored FDG uptake above surrounding tissue (visual score ≥ 1) resulted in an 83% sensitivity and 75% specificity for diagnosing C-GCA. When only high intensity uptake (visual score = 2) was considered, sensitivity decreased to 58% and increased specificity to 96%. Fig. 1 shows example images of the visual scoring assessment.

Table 1
US, ultrasound; FDG-PET/CT, Fluorine-18-fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography; CI, confidence interval; TIA, transient ischaemic attack; CVA, cerebrovascular accident; SD, standard deviation; CPR, c-reactive protein; TAB, temporal artery biopsy; GC, glucocorticoid; IQR, interquartile range.

Number of patients	24
Demographics	
Female gender	12 (50%)
Age, years [mean (SD)]	71 (8)
Symptoms	
Cranial symptoms	21 (88%)
New or different headache	18 (75%)
Scalp tenderness	8 (33%)
Temporal artery tenderness	5 (21%)
Jaw claudication	7 (29%)
TIA/CVA	2 (8%)
Constitutional symptoms	19 (80%)
Fever	6 (25%)
Weight loss	13 (54%)
Night sweats	12 (50%)
Arm claudication	2 (8%)
Leg claudication	4 (17%)
Diagnostics	
Serum CRP, mg/L [median (95% CI)]	73 (37-110)
Temporal artery biopsy	24 (100%)
Adventitial pattern	3 (13%)
Adventitial invasive pattern	3 (13%)
Concentric bilayer pattern	1 (4%)
Panarteritic pattern	17 (71%)
Duplex Ultrasound	15 (63%)
Positive Duplex ultrasound	9 (60%)*
FDG-PET/CT	
Number of patients concurrently on GC treatment	3
Serum glucose, mmol/L [median (IQR)]	6.1 (5.7-6.8*)
Days since treatment initiation [median (range)]	2 (1-3)
Number of days from PET/CT to TAB [median (IQR)]	4 (-1-9**)
Patients with LV involvement on FDG-PET/CT	15

* the GCA group included three patients whose serum glucose levels exceeded 7 mmol/L.
**the GCA group included two patients who had TAB performed 2 and 6 years prior to the FDGPET/CT scan. FDG-PET/CT was performed because of a suspected clinical recurrence. In both cases, FDG-PET/CT confirmed active LV-GCA

Cross tabulation for visual assessment results are shown in Table 2 and shows that higher FDG uptake most frequently involves the TA and least frequently involves the OA. Out of the 24 biopsied TAs, 14 were regarded positive (visual score ≥ 1) on visual assessment. In 5 patients showing no FDG uptake in the biopsied TAs, there was involvement of other cranial arteries. Additionally, 9 patients showing TA FDG uptake also showed involvement in other arteries. On visual assessment 9 patients showed bilateral TA involvement and 3 showed unilateral involvement of the non-biopsied TA. Further analysis showed that in 13 of the 24 C-GCA cases, multiple distinct arterial regions were affected, whereas the control group only had single positive arterial regions.

Performance of semiquantitative assessment of cranial artery inflammation

A ROC analysis of the highest measured SUVmax in both GCA and control cases revealed an area under the curve (AUC) of 0.88 ($CI_{95\%}$=0.77-0.99), attributing to a 79% sensitivity and a 92% specificity for a cut-off SUVmax of 5.00 (Fig. 3). ROC analysis of target-to-background ratio of the cranial arteries SUVmax divided by the SVC SUVmax resulted in an AUC of 0.84.

The image below in Fig. 3 shows sub-analysis ROC curves for the cranial arteries. Highest AUC was attained by the VA and the lowest by the OA. Table 3 shows a cross-tabulation of the results of

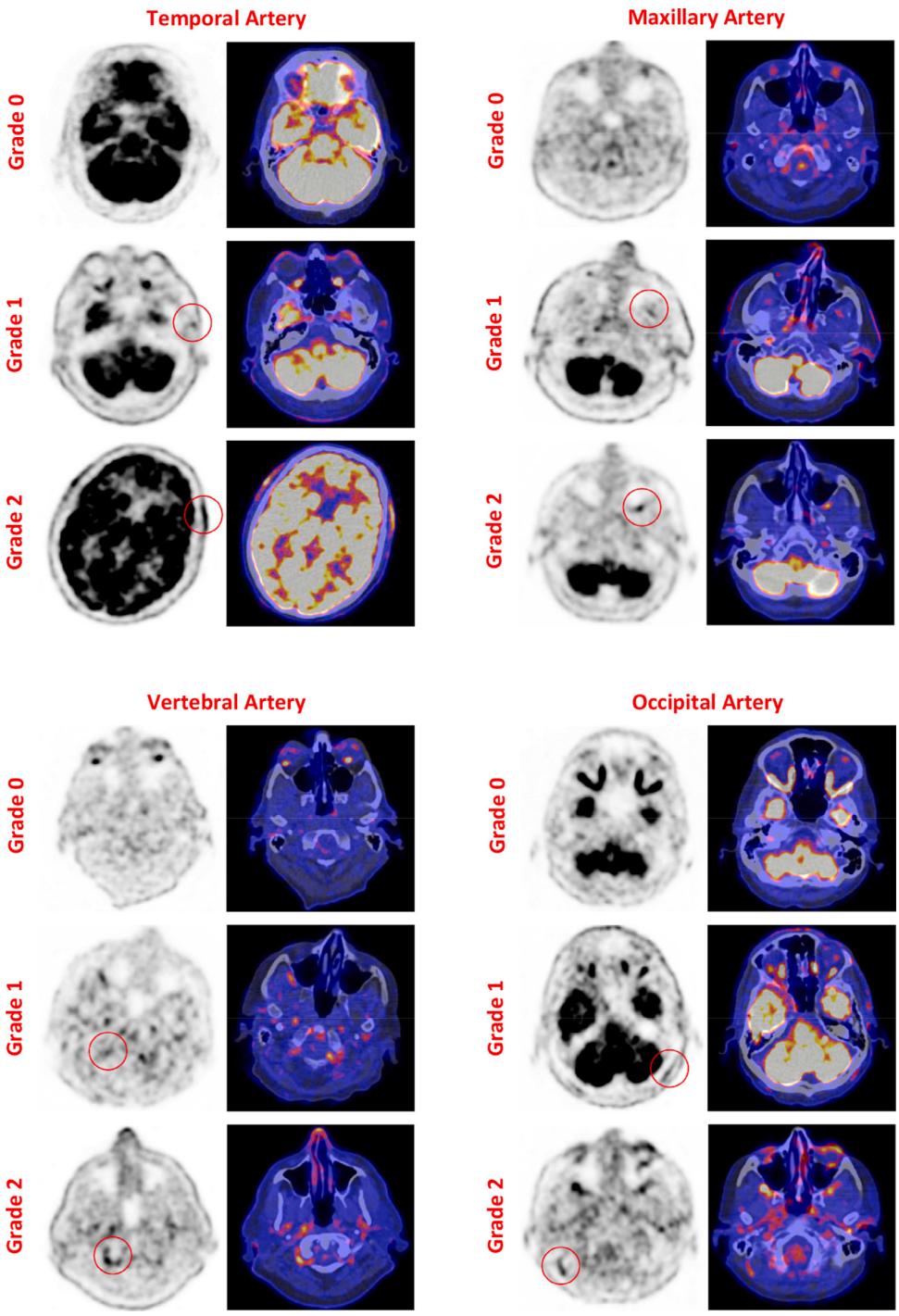

Fig. 1. Visual assessment of cranial artery inflammation on FDG-PET/CT. Temporal Artery (TA), Maxillary Artery (MA), Vertebral Artery (VA), and Occipital Artery (OA) were bilaterally visually scored from 0-2. Scoring definition: 0: no uptake above surrounding tissue; 1: uptake just above surrounding tissue; 2: uptake significantly above surrounding tissue. The red circle denotes the visually determined area of increased uptake.

semiquantitative assessment when using a SUVmax cut-off value of 5.00, showing the VA was most affected. Out of the 24 biopsy-positive TA, 9 had a SUVmax higher than 5.00 on semiquantitative assessment. In 10 patients showing no involvement of the biopsied TAs, there was involvement of other cranial arteries. Additionally, 8 patients showing involvement in the biopsied TAs also showed involvement in other arteries. Bilateral TA involvement was present in 2 cases and 2 others showed unilateral involvement of the non-biopsied TA. Furthermore, in 12 out of 24 of the cases, the SUVmax was higher than 5.00 in more than one arterial region, whereas positive controls each presented a SUVmax higher than 5.00 in only one arterial region.

Association of cranial artery assessment and large vessel assessment

Out of the 24 C-GCA patients, 15 showed large artery involvement on FDG-PET/CT. Six patients showed only cranial artery involvement. In three patients, there was neither large artery nor cranial artery involvement on FDG-PET/CT.

Comparison of visual and semiquantitative FDG-PET/CT assessments

In 37 (77%) out of all 48 subjects, the visual and semiquantitative method agreed on the presence of cranial artery uptake, defined as

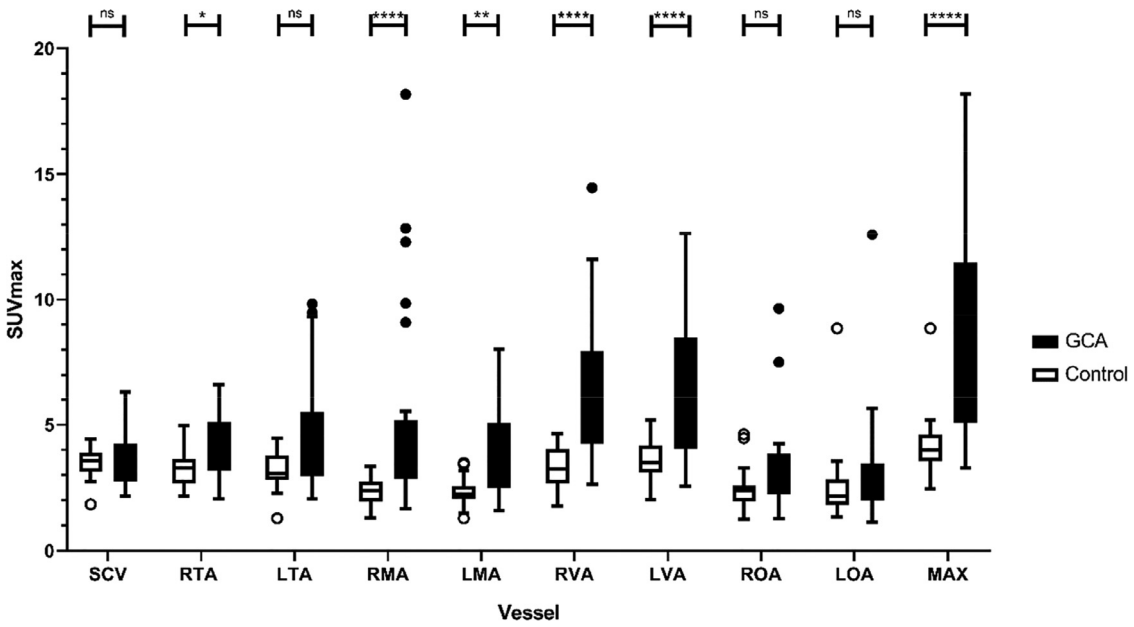

Fig. 2. Data of measured SUV max values of each vessel in boxplots. Each box represents the 25th to 75th percentiles, outliers (>1.5 × Q1,Q3) are represented as dots. Results Mann-Whitney U: ns, p>0.05; * p≤0.05; ** p≤0.01; *** p≤0.001; **** p≤0.0001. SCV, superior caval vein; RTA, right temporal artery; LTA, left temporal artery; RMA, right maxillary artery; LMA, left maxillary artery; RVA, right vertebral artery; LVA, left vertebral artery; ROA, right occipital artery; LOA, left occipital artery; MAX, highest SUVmax in the assessed cranial arteries.

Table 2
Cross tabulation of the results of visual assessment of FDG uptake in the cranial arteries. Results for bilaterally assessed cranial arteries, combinations of cranial arteries, and sensitivity and specificity are shown. TA, temporal artery; MA, maxillary artery; VA, vertebral artery; OA, occipital artery; $CI_{95\%}$, 95% confidence interval.

Cranial Artery:	Visual Assessment	GCA	Control	Sensitivity ($CI_{95\%}$)	Specificity ($CI_{95\%}$)
TA/MA/VA/OA	Positive	20	6	83% (64-93)	75% (55-88)
	Negative	4	18		
TA	Positive	18	2	75% (55-88)	92% (74-99)
	Negative	6	22		
MA	Positive	12	1	50% (31-69)	96% (80-100)
	Negative	12	21		
VA	Positive	10	0	41% (24-61)	100% (86-100)
	Negative	14	24		
OA	Positive	7	2	29% (15-49)	92% (74-99)
	Negative	17	22		
MA/VA/OA	Positive	15	4	63% (43-79)	83% (64-93)
	Negative	9	20		
TA/MA/VA	Positive	20	4	83% (64-93)	83% (64-93)
	Negative	4	20		
TA/MA/OA	Positive	20	6	83% (64-93)	75% (55-88)
	Negative	4	18		

visual score ≥ 1 and SUVmax ≥ 5.00. This resulted in a Cohen's kappa of 0.55 ($CI_{95\%}$: 0.32-0.78), which is considered moderate agreement.

Association of symptoms and FDG-PET/CT assessment

Table 4 shows a cross-tabulation of the presence of cranial symptoms and the results of the visual and semiquantitative FDG-PET/CT assessments. 90% of patients presenting with cranial symptoms had a positive (SUVmax ≥ 5.00) semiquantitative cranial artery assessment, whereas all patients presenting without cranial symptoms showed a negative (SUVmax < 5.00) semiquantitative cranial artery assessment. Two patients presenting without cranial symptoms had positive visual assessment of the cranial arteries.

There was a positive correlation between the number of cranial symptoms and the highest measured SUVmax in the cranial arteries (r=0.4179, p=0.0421). Additionally, a higher number of cranial symptoms was associated with a higher SUVmax in the VA (r=0.5492, p=0.0054) (Fig. 4).

None of the individual cranial symptoms were associated with increased uptake in any of the cranial arterial regions. Moreover, there was no correlation between the number of cranial symptoms and the number of affected arteries.

Association of Duplex Ultrasound and FDG-PET/CT assessment

Fisher's exact test revealed no significant results in cross tabulations of the visual and quantitative assessments with Duplex US result (Table 5).

Discussion

The current study is the first to investigate the diagnostic accuracy of FDG-PET/CT in biopsy proven C-GCA patients using both visual and

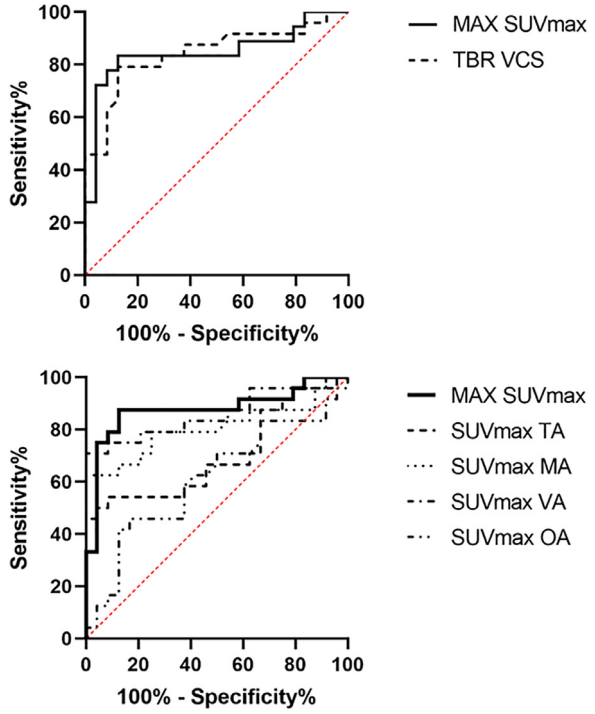

Fig. 3. Above: ROC curve of the highest (MAX) SUVmax and SUVmax SCV ratio (highest measured SUVmax in all cranial arteries divided by SUVmax of blood pool in superior caval vein). AUC values were calculated as 0.88 and 0.84 respectively. A SUVmax cut-off value of 5.0 resulted in a sensitivity of 79% and a specificity of 92% ($p<0.0001$). Below: ROC curve of the highest measured SUVmax values in all cranial arteries (MAX SUVmax), and in the temporal artery (TA), maxillary artery (MA), vertebral artery (VA), and occipital artery (OA) separately. AUC values were calculated as 0.88 for MAX SUVmax, and 0.70 (TA), 0.80 (MA), 0.85 (VA), and 0.61 (OA).

semiquantitative methods. In this specific research setting, using an SUVmax cut-off value of 5.00 resulted in a 79% sensitivity and a 92% specificity for C-GCA. Visual assessment showed a notably lower 75% specificity, underlining the importance of objective measurements. The presence of high intensity FDG uptake (visual score = 2) improved specificity to 96%%and involvement of multiple arterial regions improved specificity to 100%. Additionally, increased SUVmax in the cranial arteries was associated with the presence of cranial symptoms. These results show that FDG-PET/CT can be used to diagnose C-GCA. Due to especially the excellent obtained specificity in both this and other studies, FDG-PET/CT may provide a valuable alternative to TAB [13, 14].

Until recently, FDG-PET/CT was considered unsuitable for the detection of cranial artery inflammation, yet desirable in order to expand the range of diagnostic tools [8,11,12]. Higher resolution scanners employing time-of-flight (TOF) imaging may be the reason for improved detectability [17]. The sensitivity of the visual and semiquantitative assessments was comparable with previous studies on visual assessment of the cranial arteries on FDG-PET/CT. The 75% specificity found on visual assessment in this study is notable lower than in other FDG-PET/CT studies [13,14]. This may be due to differences in PET reconstruction and the use of one instead of multiple trained observers in this study. Because of low visibility and complex anatomical locations of the scored arteries, specifically training the observers to assess the cranial arteries is likely to improve sensitivity and specificity.

Whereas visual assessment used a more global interpretation of the FDG-PET/CT image, semiquantitative assessment was based solely on uptake intensity (SUVmax) in the cranial arteries. Both previously mentioned studies of FDG-PET/CT in C-GCA mentioned that highest accuracy can be attained when using global interpretation [13,14]. Although global interpretation is instrumental for diagnosis, this study affirms that the use of standardised objective methods of measurement and interpretation cannot be dismissed. Especially the superior specificity found when using SUVmax measurements provides a rationale to increase the use of subjective FDG-PET assessment methods. This standardisation is equally important to ensure quality and reproducibility. Additionally, because the assessment methods showed only moderate agreement, combining global interpretation and SUVmax measurements may improve diagnostic accuracy even further [18].

This study also included specific data on the assessment of the TA, MA, VA, and OA. Although this study exclusively included TAB positive cases, visual and semiquantitative PET assessments revealed positivity for the biopsied TA in only 58% and 38% of cases, respectively. This indicates a difference between histopathological (TAB) and

Table 3
Cross tabulation of the results of the semiquantitative assessment of the cranial arteries.

Cranial Artery:	SUVmax≥5.00	GCA	Control	Sensitivity ($CI_{95\%}$)	Specificity ($CI_{95\%}$)
TA/MA/VA/OA	Positive	19	2	79% (60-91)	92% (74-99)
	Negative	5	22		
TA	Positive	11	0	46% (28-65)	100% (86-100)
	Negative	13	24		
MA	Positive	7	0	29% (15-49)	100% (86-100)
	Negative	17	24		
VA	Positive	17	1	71% (51-85)	96% (80-100)
	Negative	7	23		
OA	Positive	3	1	13% (4-31)	96% (80-100)
	Negative	21	23		
MA/VA/OA	Positive	17	2	71% (51-85)	92% (74-99)
	Negative	7	22		
TA/MA/VA	Positive	19	1	79% (60-91)	96% (80-100)
	Negative	5	23		
TA/MA/OA	Positive	13	1	54% (35-72)	96% (80-100)
	Negative	11	23		

SUVmax≥5.00 was considered positive and SUVmax<5.00 negative. Results for bilaterally assessed cranial arteries, combinations of cranial arteries, and sensitivity and specificity are shown. TA, temporal artery; MA, maxillary artery; VA, vertebral artery; OA, occipital artery; $CI_{95\%}$, 95% confidence interval.

Table 4
Cross tabulation of the FDG-PET/CT assessments and presence of cranial symptoms. Semiquantitative (SUVmax) and visual assessments are shown separately.

	*SUVmax ≥ 5.00 (positive)	*SUVmax < 5.00 (negative)	**Visually positive	**Visually negative
Cranial symptoms present	19	2	18	3
Cranial symptoms absent	0	3	2	1
Total	19	5	20	4

*Highest SUVmax of the TA/MA/VA/OA
**TA/MA/VA/OA assessed.

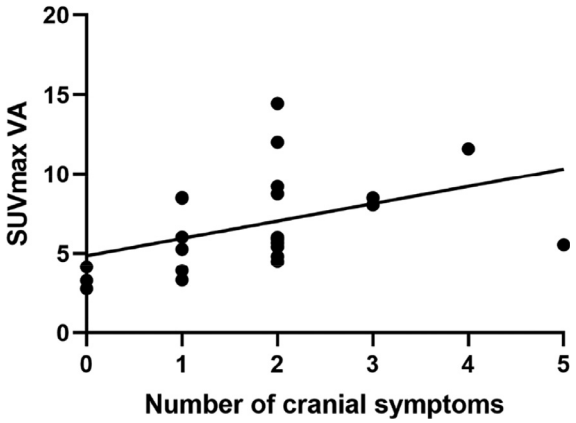

Fig. 4. Plot of the number of cranial symptoms on the *x*-axis and the SUVmax in the vertebral artery (VA) on the *y*-axis. Spearman's rho concluded a positive correlation, r=0.5492, p=0.0054.

FDG-PET/CT may provide additional value because, like TAB, US and FDG-PET of the cranial arteries may visualise different signs of inflammation.

This study has some limitations. The retrospective nature and data collection of the study are prone to bias and error. The C-GCA group included three patients with serum glucose levels exceeding 7 mmol/L, which may have lowered vascular FDG uptake in these patients and therefore have understated the results. Additionally, it is worth noting that because TAB is the only diagnostic method to definitively prove C-GCA, inflammation in other arteries than the TA could not be histologically validated. Including TAB negative C-GCA patients fell outside the scope of this study because a negative TAB does not exclude C-GCA. Moreover, some included patients underwent TAB before FDG-PET/CT, which can result in increased uptake at the location of this surgical procedure. However, of the 4 out of 5 patients in this study who had TAB performed before FDG-PET/CT, multiple arteries were assessed as positive, both on visual and semiquantitative

Table 5
Cross tabulation of the result of the Duplex ultrasound (US) result and FDG-PET/CT assessment of the cranial arteries. Semiquantitative (SUVmax) and visual assessments are shown separately.

	*SUVmax ≥ 5,0 (positive)	*SUVmax < 5,0 (negative)	**Visually positive	**Visually negative
Duplex US positive	7	2	7	2
Duplex US negative	5	1	5	1

*Highest SUVmax of the TA/MA/VA/OA;
**TA/MA/VA/OA assessed.

metabolic (FDG-PET) signs of vasculitis. This is in agreement with the study by Nielsen et al., who found that in their TAB positive patient group, only 51% had positive TA on FDG-PET/CT [13].

Although much is known about the involvement of the TA, involvement of the VA is less well documented. This study found high diagnostic accuracy for C-GCA when solely using semiquantitative assessment of the VA (AUC = 0.85). This is also reflected in the study by Nielsen et al., where the most frequently affected artery was the VA [13]. Several US studies show frequent involvement of the VA in C-GCA. Occlusion of the VA can cause severe neurological manifestations [19,20]. A correlation between the number of reported cranial symptoms and the FDG uptake in the VA in this study further highlights the importance of assessment of these arteries.

Since recent years, clinicians increasingly rely on US as a diagnostic tool for C-GCA. Results from a large study on US for diagnosing C-GCA showed a 54% sensitivity and 81% specificity. The diagnostic accuracy of US is highly dependent on the examiner's skill, whereas in FDG-PET/CT cranial artery assessment likely requires less additional training [13,14]. Additionally, FDG-PET/CT imaging is generally used next to US already to diagnose LV-GCA. Results from this study suggest that cranial artery assessment on FDG-PET/CT provides an alternative to US, by attaining better diagnostic accuracy, showing involvement of additional cranial arteries, and decreasing the number of diagnostic tests needed. Moreover, as presented in Table 5, assessment. Regarding semiquantitative assessment, comparing SUVmax between different arteries as performed in this study is complicated because the TA and VA inherently show higher SUVs, also in the control group. Despite these inherent differences, the diagnostic accuracy combining all arteries was superior to that of individual arteries, signifying that GCA patients can have comparably high SUVmax along all four arteries. Lastly, results from this study may not be generalisable to centres with less expertise in vascular assessment on FDG-PET/CT. However, assessment in this study was in line with previous work, which concluded high interobserver agreement after only short training [13].

In conclusion, this study further strengthens the evidence that FDG-PET/CT can be used along the entire spectrum of GCA, diagnosing isolated C-GCA in addition to concurrent and isolated LV-GCA. Expanding the use of FDG-PET/CT to the cranial arteries increases diagnostic accuracy for C-GCA and its high specificity may make it a suitable alternative to TAB. Additionally, the diagnostic performance of semiquantitative assessment provides a rationale to increase the clinical use of standardised objective methods in the diagnosis of vasculitis.

Declaration of competing interest

Dr. E. Brouwer, as an employee of the UMCG, received speaker fees and consulting fees from Roche in 2017 and 2018, which were paid to the UMCG. The other authors declare no conflicts of interest.

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