Large vessel vasculitis in giant cell arteritis and polymyalgia rheumatica – prevalence, outcome and associated factors

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Abbreviations

ACR	American College of Rheumatology
AION	anterior ischemic optic neuropathy
BARK	Basler Riesenzellarteriitis Kohorte
BMI	body mass index
CI	confidence interval
CRAO	central retinal artery occlusion
CRP	C-reactive protein
CT	computed tomography
CVI	cerebrovascular insult
EKNZ	ethics commission northwest Switzerland
ESR	erythrocyte sedimentation rate
EULAR	European Alliance of Associations for Rheumatology
FDG	[^{18}F]fluorodeoxyglucose
FSRMM	Swiss Foundation for Research on Muscle Diseases
GCA	giant cell arteritis
GP	general practitioner
GRASP	Golden-angle RAdial Sparse Parallel
IMT	intima media thickness
INOP	internuclear ophthalmoplegia
IPD	individual patient data

IQR	interquartile range
LV-GCA	large vessel giant cell arteritis
LVV	large vessel vasculitis
MMP-3	matrix metalloprotease-3
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
NA	not available
OGUS	OMERACT Giant cell arteritis Ultrasonography Score
OMERACT	Outcome Measures in Rheumatology
OR	odds ratio
PET	positron emission tomography
PET/CT	[^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography
PETVAS	positron emission tomography vascular activity score
PION	posterior ischemic optic neuropathy
PMR	polymyalgia rheumatica
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PVL	permanent vision loss
QUADAS	Quality Assessment of Diagnostic Studies
SCQM	Swiss Clinical Quality Management in Rheumatic Diseases
SD	standard deviation
SUV	standardized uptake value

TA	temporal artery
TAB	temporal artery biopsy
TAK	Takayasu’s arteritis
TVI	transient visual impairment
TVS	total vascular score
US	ultrasound

Summary

English summary

Background: Giant cell arteritis (GCA) is the most common primary vasculitis of the elderly and is closely related to polymyalgia rheumatica (PMR). Both conditions may occur separately, simultaneously, or sequentially over time. GCA classically manifests as cranial arteritis, but large vessel vasculitis (LVV) has been recognized as part of the disease spectrum. Diagnosing LVV remains challenging as symptoms may be non-specific and imaging is necessary to establish the diagnosis. Furthermore, PMR may be the only clinical manifestation of GCA. However, the understanding of subclinical GCA in patients with PMR, including its prevalence, risk factors and prognostic significance, is limited.

GCA is associated with severe vascular and ischemic complications such as stroke, arterial stenosis, and the development of aortic aneurysms. The most feared complication of GCA is permanent vision loss, and timely diagnosis and treatment of GCA are crucial to prevent acute and chronic complications. Although fast-track clinics for GCA have reduced the delay in diagnosis, permanent vision loss is still reported in up to 13% of cases.

Established imaging modalities for the diagnosis of LVV include ultrasound, [^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT), CT, or magnetic resonance imaging (MRI). However, standardized criteria defining vasculitis on MRI are lacking. While imaging is well established in the diagnostic work-up of patients with suspected GCA, its role in monitoring disease activity during follow-up and predicting the disease course in GCA after treatment discontinuation remains unclear. As relapses are common in patients with GCA after treatment withdrawal, imaging biomarkers for guiding the timing of treatment stop would be helpful.

Objectives: We first aimed to investigate the prevalence of subclinical GCA in patients with newly diagnosed PMR in the literature and to identify potential patient characteristics associated with subclinical GCA in published cohorts. In a next step, we aimed to explore the hypothesis that undiagnosed subclinical GCA in patients with PMR may lead to GCA-associated vascular damage. In our second manuscript, we aimed to study the risk factors and incidence of permanent vision loss in patients with GCA and to identify obstacles which caused a delay in diagnosis. The third manuscript aimed to identify which parameters on MRI correspond to vasculitis in patients with newly diagnosed large vessel (LV-) GCA. Finally, we addressed the role of PET/CT and MRI to predict relapses after treatment stop in patients with large vessel LV-GCA.

Methods: We systematically searched PubMed, Embase, and Web of Science Core Collection for consecutively recruited cohort studies reporting the prevalence of GCA in steroid-naïve patients with PMR. Potential predictors of subclinical GCA were identified using individual patient data from seven cohorts.

In the frame of our retrospective cohort of patients with GCA, we investigated the hypothesis that a proportion of patients with newly diagnosed GCA and a history of PMR may have already had subclinical GCA at the time of PMR manifestation and compared vascular ultrasound findings (extent of vessel involvement and stenoses) between GCA patients with and without prior PMR. Furthermore, we used our retrospective cohort to examine patient and referral characteristics and trends in the incidence of permanent vision loss over the past 15 years at the University Hospital Basel.

To identify which parameters on MRI correspond to vasculitis in patients with newly diagnosed LV-GCA, we compared MRI findings to PET/CT and/or ultrasound findings on a segment level (axillary segment per side, and the thoracic aorta).

Lastly, in an exploratory cohort study, patients with LV-GCA underwent imaging at the time of treatment discontinuation. Imaging findings of patients who relapsed within 4 months after treatment discontinuation were compared to those who remained in remission.

Results: The pooled prevalence of subclinical GCA across all identified studies was 23%, and 29% in the studies using PET/CT. Inflammatory back pain and absence of lower limb pain remained weak predictors of subclinical GCA after multivariable analysis.

Newly diagnosed patients with GCA and a prior history of PMR had significantly more often LVV (51.0% vs. 25.0%, $p<0.001$) and stenosis within the vasculitic segments (18.4% vs. 3.1%, $p<0.001$) on ultrasound compared to patients without prior PMR in our retrospective cohort.

The incidence of permanent vision loss was 17.4% in our institution and did not decline over 15 years. More than half of the patients who suffered from vision loss had experienced non-ocular symptoms related to GCA for a median of 21 days but did not seek medical help until the onset of visual impairment. In multivariable analysis, patients with vision loss were older and reported more frequently jaw claudication.

Vessel wall oedema on diffusion-weighted sequences on MRI corresponded to vasculitic PET/CT findings while pathological vessel segments on MRI had a low agreement with vasculitic ultrasound findings.

None of the examined imaging parameters predicted subsequent relapse after treatment withdrawal in patients with LV-GCA. The number of segments with vasculitic findings on PET/CT and the sum of all maximum standardized uptake value (SUV_{max}) artery/liver ratios showed a slight tendency to be higher in patients who relapsed; however, this did not reach statistical significance.

Conclusion: The high prevalence of subclinical GCA and the accumulating evidence of the potential impact of subclinical GCA on disease outcome advocates a paradigm shift in the assessment of patients with PMR and supports the implementation of screening strategies for

large vessel involvement. Our findings underscore the need to increase public and physician awareness of the potentially devastating consequences of GCA and the importance of early detection and timely medical treatment to further reduce the incidence of ischemic and vascular complications. Lastly, we did not find any parameter on imaging performed at the time of treatment discontinuation which predicted future relapse in patients with LV-GCA. The relevance of vasculitic imaging findings in patients in clinical remission of GCA for the development of aortic aneurysms should be further studied.

Deutsche Zusammenfassung

Hintergrund: Die Riesenzellarteriitis (RZA) ist die häufigste primäre Vaskulitis des älteren Menschen und ist eng mit der Polymyalgia rheumatica (PMR) verwandt. Beide Erkrankungen können getrennt, gleichzeitig oder nacheinander auftreten. Die RZA befällt klassischerweise die kranialen Gefässe, aber auch eine Entzündung der grossen Gefässe ist als Teil des Krankheitsspektrum anerkannt. Die Diagnose der Grossgefässvaskulitis ist jedoch nach wie vor schwierig, da die Symptome unspezifisch sein können und eine Bildgebung zur Diagnosestellung notwendig ist. Die PMR kann zudem die einzige klinische Manifestation einer zugrundeliegenden RZA sein. Der Kenntnisstand über die Prävalenz, Risikofaktoren und prognostische Bedeutung der subklinischen RZA ist jedoch begrenzt.

Die RZA ist mit schwerwiegenden vaskulären und ischämischen Komplikationen, wie Schlaganfall, arteriellen Stenosen, oder Aortenaneurysmen assoziiert. Die gefürchtetste Komplikation der RZA ist der permanente Sehverlust und eine schnelle Diagnose sowie Behandlung der RZA ist entscheidend, um akute und chronische Komplikationen zu verhindern. Obwohl die Etablierung von Fast-Track Kliniken die Zeit bis zur Diagnosestellung verkürzt hat, tritt immer noch in bis zu 13% der Fälle ein dauerhafter Sehverlust auf.

Zu den etablierten bildgebenden Verfahren in der Diagnose der Grossgefässvaskulitis gehören der Ultraschall, die Computertomographie (CT), die [^{18}F]Fluordesoxyglucose Positronen-Emissions-Tomographie/CT (PET/CT), oder die Magnetresonanztomographie (MRT). Bis heute gibt es jedoch keine standardisierten Kriterien, um die Grossgefässvaskulitis im MRT zu diagnostizieren.

Während die Bildgebung bei der Diagnosestellung der RZA fest etabliert ist, bleibt ihre Rolle beim Monitoring der Krankheitsaktivität unter Therapie sowie ihr Einsatz zur Vorhersage des Krankheitsverlaufs nach Absetzen der Behandlung unklar. Da Patient:innen mit RZA nach

Therapiestopp häufig rezidivieren, wären Parameter aus der Bildgebung hilfreich, um den Zeitpunkt des Behandlungsstopp individuell bestimmen zu können.

Ziele: In einer systematischen Literaturübersicht und Metaanalyse individueller Patientendaten untersuchten wir die Prävalenz und Risikofaktoren einer subklinischen RZA bei Patient:innen mit neu diagnostizierter PMR. In einem nächsten Schritt untersuchten wir die Hypothese, dass eine nicht diagnostizierte subklinische RZA bei Patient:innen mit PMR zu RZA-assoziierten Gefässschäden führen kann. In unserem zweiten Manuskript untersuchten wir die Inzidenz des permanenten Sehverlusts bei Patient:innen mit RZA innerhalb von 6 Monaten nach Diagnose, sowie die Faktoren im Krankheitsverlauf, welche zu einer Verzögerung der Diagnose geführt haben. Das Ziel des dritten Manuskripts war es herauszufinden, welche Parameter im MRT einer Grossgefässvaskulitis entsprechen. In unserem letzten Manuskript untersuchten wir die Rolle von PET/CT und MRT in der Vorhersage von Rezidiven nach Therapiestopp bei RZA Patient:innen mit einer Grossgefässbeteiligung.

Methoden: Wir durchsuchten systematisch PubMed, Embase und Web of Science Core Collection nach konsekutiv rekrutierten Kohortenstudien, die über die Prävalenz der RZA bei steroidnaiven Patient:innen mit PMR berichteten. Potenzielle Prädiktoren für eine subklinische RZA wurden anhand individueller Patientendaten aus sieben Kohorten untersucht.
Wir stellten die Hypothese auf, dass ein Teil der Patient:innen mit einer neu diagnostizierten RZA und PMR in der Vorgeschichte bereits zum Zeitpunkt der PMR Manifestation eine subklinische RZA gehabt haben könnte. Wir etablierten eine retrospektive Kohorte mit Patient:innen, die wegen Verdachts auf RZA eine Ultraschalluntersuchung erhalten haben, und verglichen die sonographischen Resultate (Ausmass der Grossgefässbeteiligung und arterielle Stenosen) zwischen Patient:innen mit und ohne PMR in der Vorgeschichte. Darüber hinaus nutzten wir unsere retrospektive Kohorte, um Trends in der Inzidenz in den letzten 15 Jahren sowie Risikofaktoren des Sehverlusts am Universitätsspital Basel zu untersuchen.

Um herauszufinden, welche MRT-Parameter einer Vaskulitis entsprechen, verglichen wir MRT-Befunde mit PET/CT- sowie Ultraschallbefunden auf Segmentebene (axilläres Segment pro Seite; thorakale Aorta). In einer explorativen Kohortenstudie führten wir bei Patient:innen mit RZA und Grossgefässbeteiligung zum Zeitpunkt des geplanten Therapiestopps eine PET/CT- und/oder MRT-Untersuchung durch und verglichen die Ergebnisse der Bildgebung zwischen Patient:innen, welche innerhalb von 4 Monaten nach Absetzen der Behandlung ein Rezidiv erlitten mit denjenigen Patient:innen, welche in Remission blieben.

Resultate: Die gepoolte Prävalenz der subklinischen RZA aus allen identifizierten Studien lag bei 23%. In den Studien, in denen ein PET/CT eingesetzt wurde, lag die Prävalenz bei 29%. Entzündliche Rückenschmerzen und das Fehlen von Schmerzen in den unteren Gliedmassen waren die einzigen statistisch signifikanten Prädiktoren für eine subklinische RZA in der multivariablen Analyse.

Neu diagnostizierte Patient:innen mit RZA und einer PMR in der Vorgeschichte wiesen signifikant häufiger eine Grossgefässbeteiligung (51.0% vs. 25.0%, $p<0.001$) und vaskulitische Gefässstenosen (18.4% vs. 3.1%, $p<0.001$) im Ultraschall auf als Patient:innen ohne PMR in der Vorgeschichte.

Die Inzidenz des dauerhaften Sehverlusts in unserem Institut lag bei 17.4% und nahm über den Verlauf von 15 Jahren hinweg nicht ab. Mehr als die Hälfte der Patient:innen, welche einen Sehverlust erlitten, hatten im Median 21 Tage lang RZA-assoziierte Symptome, suchten aber bis zum Auftreten des Sehverlusts keine medizinische Hilfe auf. In der multivariablen Analyse waren Patient:innen mit Sehverlust älter, und berichteten häufiger über eine Kieferklaudikatio. Gefässwandödeme in diffusionsgewichteten Sequenzen im MRT stimmten am häufigsten mit vaskulitischen PET/CT-Befunden überein, während pathologische Gefässsegmente im MRT eine geringe Übereinstimmung mit vaskulitischen Ultraschallbefunden aufwiesen.

Keiner der untersuchten bildgebenden Parameter konnte ein späteres Rezidiv nach Therapiestopp bei Patient:innen mit RZA und Grossgefässbeteiligung vorhersagen. Es wurde eine Tendenz zu einer höheren Anzahl von Segmenten mit vaskulitischen Befunden im PET/CT bei Patient:innen mit Rezidiv sowie grössere Summe aller SUV_{max} («standardized uptake value») Arterie-zu-Leber-Verhältnisse festgestellt, ohne jedoch eine statistische Signifikanz zu erreichen.

Schlussfolgerung: Die hohe Prävalenz der subklinischen RZA und die zunehmende Evidenz für ihre Auswirkungen auf den Krankheitsverlauf bei PMR sprechen für einen Paradigmenwechsel in der Beurteilung der Patient:innen und unterstützen die Einführung von Screening-Strategien der grossen Gefässe. Unsere Ergebnisse unterstreichen die Notwendigkeit, sowohl die Öffentlichkeit als auch die Ärzteschaft für die potenziell verheerenden Folgen der RZA zu sensibilisieren und die Bedeutung einer frühzeitigen Erkennung und Behandlung hervorzuheben, um die Inzidenz der ischämischen sowie vaskulären Komplikationen zu reduzieren. Zum Zeitpunkt des Therapiestopps wurde in der Bildgebung bislang kein Parameter gefunden, der das Auftreten von Rezidiven bei Patient:innen mit RZA mit Großgefässbeteiligung vorhersagen kann. Die Relevanz von vaskulitischen Bildgebungsbefunden bei Therapiestopp für die Entwicklung von Aortenaneurysmen bei Patient:innen in klinischer Remission sollte weiter untersucht werden.

1 Introduction

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are two common and overlapping inflammatory conditions affecting individuals over the age of 50 years (1). The highest incidence is found in individuals of Northern European ancestry, particularly those from Scandinavian countries (2–4).

PMR occurs two to three times more often than GCA, and primarily affects articular and periarticular structures causing bilateral shoulder and hip girdle pain, morning stiffness, and a systemic acute phase response (5–8). GCA is the most common primary vasculitis which involves medium- and large-sized arteries, preferentially the supra-aortic branches (1,9). The spectrum of GCA comprises a number of distinct and overlapping phenotypes and the clinical picture depends on the vascular region affected (10–12). The vasculitic involvement of the cranial vessels leads to the classic symptoms of GCA such as headache, jaw claudication, scalp tenderness, abnormalities of the temporal arteries or visual impairment. In contrast, individuals with large vessel involvement predominantly show nonspecific symptoms such as fever, weight loss or polymyalgia (1). GCA can lead to severe complications, including permanent vision loss or ischemic stroke (13,14). Large vessel involvement has been associated with chronic vascular complications such as arterial stenosis, large artery dissection or the development of aortic aneurysms (15,16).

Disease-specific markers are lacking for both PMR and GCA, and the diagnosis is based on a combination of clinical symptoms, elevated inflammatory markers and exclusion of differential diagnoses (17). Temporal artery biopsy is considered the gold standard for diagnosing GCA (18,19). In recent years, however, vascular imaging has increasingly replaced temporal artery biopsy because imaging is less invasive and more sensitive, covering a wide range of vascular regions and allowing the diagnosis of patients with exclusively extracranial large vessel disease (20,21).

Treatment of both conditions is based on long-term glucocorticoid therapy. In isolated PMR, an initial dose of 12.5 mg to a maximum of 25 mg per day of prednisone equivalent are recommended to induce remission, while considerably higher doses are given to control disease activity and prevent ischemic complications in GCA (starting dose 1 mg/kg body weight) (22–24). On the one hand, although glucocorticoids are effective in relieving disease-specific symptoms, prolonged glucocorticoid therapy is associated with serious adverse events such as infections, osteoporosis, diabetes or hypertension (25–30). On the other hand, relapse rates are high upon glucocorticoid tapering in both PMR and GCA (31,32). To address these challenges, efforts have been made to implement glucocorticoid sparing drugs in the treatment of PMR and GCA and to minimize the cumulative glucocorticoid dose (33). In 2018, the Swiss Agency for Therapeutic Products (Swissmedic) authorised the use of the interleukin-6 receptor alpha inhibitor tocilizumab as adjunctive therapy for patients with GCA (34–36). Tocilizumab has been shown to result in sustained remission and to have a significant steroid-sparing effect (34–36). However, current evidence only supports the use of tocilizumab as adjunctive treatment of GCA, and inconclusive results have been reported about the effects of methotrexate in both PMR and GCA (22,37–39).

1.1 Subclinical giant cell arteritis in polymyalgia rheumatica

1.1.1 Prevalence and risk factors of subclinical giant cell arteritis

The close relationship between PMR and GCA has since long been recognised (40,41). Around half of the patients with GCA report polymyalgic symptoms at diagnosis or during relapse, while other patients have a history of PMR before the onset of GCA (10). Furthermore, PMR may be the only clinical manifestation of GCA. Already in 1968, Hamrin et al. found histopathological evidence of GCA in the aorta and its branches in autopsies of patients with PMR, in whom symptoms of GCA had been absent, and therefore proposed the name

'polymyalgia arteritica' (42,43). However, this knowledge had been lost in the meantime. In 1990, the American College of Rheumatology (ACR) criteria were introduced with the intent to distinguish GCA from other vasculitides (44). These criteria ended up being widely misused to diagnose GCA, leading to the belief that GCA was primarily a headache disorder (10). It was not until the introduction of modern imaging techniques that the concept of subclinical vasculitis in PMR as part of the spectrum of GCA has experienced a renaissance (10). Imaging studies have shown that patients with PMR may have large vessel vasculitis, in the absence of specific vasculitic manifestations of GCA (45–48). However, the prevalence and characteristics of such subclinical GCA in patients with isolated PMR has not been systematically investigated.

During my PhD, we therefore performed a systematic literature review and individual patient data meta-analysis to summarize the current evidence on the prevalence and risk factors of subclinical GCA in patients with clinically isolated PMR (49). We systematically searched PubMed, Embase, and Web of Science Core Collection for consecutively recruited cohort studies reporting the prevalence of GCA in steroid-naïve patients with PMR, in whom cranial and ischemic symptoms of GCA were absent. We identified a total of 13 cohorts including 566 patients from studies which were published between 1965 and 2020 and combined the prevalences of subclinical GCA across populations in a random-effect meta-analysis. We found a pooled prevalence of subclinical GCA of 23% (95% confidence interval (CI) 14%–36%) in patients examined by either temporal artery biopsy, ultrasound or [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT). The pooled prevalence of subclinical GCA among patients screened by PET/CT was 29% (95% CI 13%–53%).

To investigate potential clinical and laboratory predictors for subclinical GCA in patients with PMR, we assembled individual patient data from seven cohorts encompassing 243 patients with newly diagnosed PMR who had been screened by PET/CT. In univariable mixed-effects logistic regression models, we found an association between routinely collected clinical and laboratory

parameters and the occurrence of subclinical GCA, such as female sex, weight loss, fever, inflammatory back pain, absence of lower limb pain, thrombocytosis, and anemia. After multivariable analysis, only inflammatory back pain (odds ratio (OR) 5.71; 95% CI 1.41–23.06) and absence of lower limb pain (OR 3.48; 95% CI 1.16–10.42) remained statistically significantly associated with subclinical GCA. However, due to the wide confidence intervals, there is uncertainty about the magnitude of the association, and external validation of these variables as predictors using other datasets is needed. Of note, we did not observe an association between subclinical GCA and markers of inflammation such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Overall, our results imply that routinely collected clinical and laboratory parameters do not reliably predict which patients may have subclinical GCA.

Very recently, efforts have been made to prospectively investigate the prevalence and characteristics of subclinical GCA in patients with PMR and since the publication of our systematic literature review, several studies have provided new data (50–54). De Miguel et al. conducted an international multicenter study, in which patients with PMR without symptoms of GCA underwent an ultrasound examination of the temporal, common carotid, subclavian and axillary arteries. Of the 346 patients included, 79 (22.8%) showed a halo sign in at least one examined artery. Schmidt et al. detected subclinical GCA in 12 of 79 isolated PMR patients (15.2%) seen at their GCA fast-track clinic between January and December 2022 (54) and preliminary data from a recent abstract reported subclinical GCA in 25.8% of PMR patients when screened by ultrasound (53). Furthermore, the study by Burg et al., which had been included in our systematic review in abstract form, has recently been published in full text, showing a high prevalence of subclinical GCA in 21.6% of patients with PMR when screened by ultrasound (51). Overall, these recent results confirm our findings that the prevalence is high, with more than a fifth of patients with newly diagnosed PMR likely to have subclinical GCA.

In the prospective study by de Miguel et al., patients with subclinical GCA were older, had a shorter duration of morning stiffness, and more often reported hip pain than patients with isolated PMR. Consistent with our findings, they did not observe an association between subclinical GCA and markers of inflammation such as CRP and ESR (50). However, this is contradicted by recent studies which demonstrated that a high ESR identified PMR patients with overlapping GCA (53,55,56).

Van Sleen et al. have recently shown and validated an association between biomarkers of angiogenesis, which are relevant to vascular inflammation, and the presence of subclinical GCA in PMR (55,56). In their studies, high angiopoietin-2 levels and angiopoietin-2/angiopoietin-2 ratios were significantly higher in patients with subclinical GCA compared to isolated PMR (55,56). Moreover, low levels of matrix metalloprotease-3 (MMP-3), an enzyme associated with synovial inflammation and joint destruction, were associated with a higher risk for a PMR/GCA overlap (56–58). The higher levels of MMP-3 in patients with isolated PMR are thought to represent a more extensive synovial inflammation compared to subclinical GCA (56). Screening for these biomarkers may therefore assist in deciding which PMR patients should undergo further evaluation for GCA (56).

1.1.2 Challenges in the management of subclinical giant cell arteritis

To date, the significance of subclinical GCA for patients with PMR is still unknown, leading to considerable uncertainty and challenges in the management of these individuals (10). It remains unclear whether patients with PMR and subclinical GCA require higher glucocorticoid doses than patients with isolated PMR (10). Furthermore, the long-term effects of subclinical GCA are not well understood. A retrospective study reported a high incidence of ischaemic complications in patients with GCA who had a history of PMR (59). In this study, 18 of 167 (11%) patients with GCA had a prior diagnosis of PMR. During follow-up, these patients developed typical cranial vasculitic symptoms and signs of upper extremity vascular

insufficiency, which led to the diagnosis of GCA. Half of these patients suffered from severe ischemic complications, including permanent vision loss, stroke and limb claudication (59). Assuming that at least some of these patients already had subclinical GCA at the time of PMR diagnosis, this finding suggests that vasculitis may have progressed during PMR treatment even in asymptomatic patients (59). Studies assessing the incidence of vascular complications such as vascular stenosis or aortic aneurysms in PMR patients with subclinical GCA are missing. Due to this lack of evidence and inconclusive results, routine screening for subclinical GCA is currently not recommended in patients with PMR (22).

1.2 Permanent vision loss in giant cell arteritis

1.2.1 The severe consequences of diagnostic delay in giant cell arteritis

Due to the vast range of clinical manifestations, diagnosis of GCA can be challenging. On the one hand, when GCA presents with typical cranial features, the diagnosis is straightforward (1). On the other hand, less frequent onset pattern and nonspecific symptoms may cause difficulty in recognising GCA and lead to a delay in diagnosis (60). However, diagnostic delay can have devastating consequences for the patient, as untreated GCA carries a substantial risk of neuro-ophthalmological complications, such as permanent vision loss or stroke (23).

Vision loss in GCA is mostly caused by damage to the posterior ciliary arteries or occlusion of the central retinal artery (1). It usually occurs early in the disease course and presents an acute ophthalmological emergency (14,61). Immediate initiation of glucocorticoid treatment upon suspicion of GCA is key in preventing vision loss (62,63). If vision is lost in one eye, there is a high risk that the fellow eye will be affected if left untreated (1). Unfortunately, the prognosis of vision loss in GCA remains poor and visual impairment is usually permanent (64).

While the mean diagnostic delay between the onset of symptoms and the diagnosis of GCA has been reported to be 9 weeks, it remains unclear which stages in the disease course contribute

most to the delay in diagnosis and therefore treatment initiation (60). On the one hand, delay may occur between symptom onset and first medical evaluation in primary care and depends on the time it takes for the patient to seek medical attention and to be given an appointment. On the other hand, there may be a delay between first consultation and final diagnosis, as it takes time for the primary care physician to suspect GCA, refer the patient for specialist assessment, and for the patient to receive a final diagnosis at a specialist center (60). Identifying which of these delays could potentially be prevented could help to further reduce the incidence of permanent vision loss (60).

1.2.2 Fast-track clinics and their impact on the incidence of permanent vision loss

The last few years have witnessed a growth in the number of fast-track clinics for early diagnosis of GCA which have been shown to reduce the diagnostic delay, mainly by shortening the time from primary care referral to specialist evaluation (65–67). These fast-track clinics reported a significant reduction in the rate of permanent vision loss compared to the conventional pathway (65–67). The incidence of permanent vision loss in patients seen in fast-track clinics has been reported to range from 2.4% to 12.7% compared to 21.5% to 37% in the conventional treatment groups (65–67). Therefore, the current recommendations for the management of large vessel vasculitis emphasize a prompt referral to specialist care of patients with symptoms and signs suggestive of GCA (23). In 2014, a fast-track clinic for patients with suspected GCA was established at the University Hospital Basel. Up to now, the impact of this fast-track pathway on the incidence of permanent vision loss in patients diagnosed with GCA at the University Hospital Basel has not been systematically studied.

1.2.3 Risk factors for permanent vision loss in giant cell arteritis

Remaining research gaps in the prevention of permanent vision loss in GCA include the identification of clinical risk factors for imminent vision loss. Although a number of studies have addressed this issue, clinical factors such as the level of inflammatory parameters, jaw

claudication, or male sex have been inconsistently associated with ocular ischemia (61,68–71). Furthermore, the association between pathological findings of the temporal arteries and permanent vision loss has been investigated in a few studies, however, conclusive results cannot be drawn (72–76). In histopathological studies of temporal artery biopsies, giant cells have been variously associated with permanent vision loss (72,73). Moreover, conflicting results have been reported on the relationship between the extent of vascular involvement on ultrasound and vision loss (75,76).

1.3 The role of imaging in large vessel giant cell arteritis

1.3.1 The implementation of imaging in the diagnosis of giant cell arteritis

In recent years, there have been substantial developments in the field of GCA. For decades, GCA has been considered a disease that mainly affects the branches of the external carotid artery, and was therefore referred to as 'temporal arteritis' (10,11). With the advent of high-resolution vascular imaging techniques, it has been recognized that arterial involvement in GCA frequently extends beyond the cranial arteries, suggesting that GCA represents a generalized vasculitic syndrome (10,77–79). Consequently, large vessel (LV-) GCA has been added to the disease definition (20). Since then, vascular imaging modalities such as ultrasound, magnetic resonance imaging (MRI), CT and PET/CT have been increasingly used in the assessment of patients with GCA (80–82). In light of these new developments, evidence-based recommendations for the use of imaging in large vessel vasculitis were developed in 2018 and incorporated in the updated European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of large vessel vasculitis (20,23). Accordingly, imaging is now recommended in all patients suspected of GCA to support the clinical diagnosis, as long as the initiation of treatment is not delayed (20). Moreover, imaging defined large vessel involvement has been included in the recently published ACR/EULAR 2022 classification

criteria for GCA, revising the previous 1990 ACR classification criteria, which mainly focused on cranial features of GCA (44,83).

However, there is still uncertainty as to which imaging modality is best for diagnosing LV-GCA, as there is no diagnostic gold standard and only few comparative studies are available (20,84). Conventional angiography has been considered the diagnostic standard for LV-GCA in the past, but it is invasive and provides no information on vessel wall morphology and is thus no longer recommended for the diagnosis of LV-GCA (19,20). Due to the absence of readily accessible biopsy sites, histological confirmation of vasculitis in the large arteries is also neither practical nor safe (84). Therefore, the EULAR recommendations state that ultrasound, CT, MRI or PET/CT may be equivalently used to support the diagnosis of LV-GCA, with ultrasound being the preferred early imaging modality (20).

1.3.2 Imaging correlates of large vessel vasculitis

Different imaging techniques measure different characteristics of the vessel wall (84). Ultrasound emits sound waves and measures the thickness of the vessel wall based on echogenicity (85). Vasculitis on ultrasound appears as homogenous, hypoechogenic, and circumferential vessel wall thickening, referred to as 'halo sign'. Furthermore, vascular stenosis and occlusion can be visualized on ultrasound (80,86). In the temporal arteries, vasculitis can be detected using the 'compression sign' (87). To standardize the interpretation of ultrasound findings, intima-media cut-off values for vasculitis have been proposed (88).

[^{18}F]FDG PET/CT is a whole-body imaging procedure which can visualize increased glucose metabolism in the vessels (46,84). FDG is a glucose analogue and radioactive tracer and is taken up by cells with high metabolic activity, allowing the detection of inflammatory processes (46). For the interpretation of PET/CT in the diagnosis of GCA, several methods have been published such as the visual comparison of vascular FDG uptake with liver uptake according to a four-grade scale, or the use of standardized uptake values (SUVs) (77,82,89–92). Recently,

SUV ratio-based cut-off values for diagnosing GCA have been published, with a high diagnostic accuracy (82,91).

On MRI, circumferential vessel wall thickening, wall oedema, and luminal stenosis have been described as correlates of cranial vasculitis, and contrast enhancement of the arterial wall presumably reflects active inflammation (81,93–95). However, to date, diagnostic criteria for LV-GCA using MRI are lacking and only few studies exist on the diagnosis of LV-GCA by MRI (89,96–101,20).

1.3.3 Imaging to monitor disease activity and predict future outcome

Relapses in LV-GCA are common, occurring in about 40% of patients during glucocorticoid tapering or after treatment withdrawal (31,102,103). It has therefore been hypothesised that the high relapse rate may be due to persistent subclinical activity in patients in apparent clinical remission (84). However, identifying patients with subclinical disease remains challenging as symptoms may be absent and inflammatory parameters may remain normal even during relapse (84,104). The introduction of tocilizumab has brought additional difficulties in monitoring disease activity and response to treatment in patients with GCA since tocilizumab suppresses the production of CRP and ESR, making these important parameters unreliable in assessing ongoing inflammatory processes (105,106).

In light of these challenges, several studies have investigated the role of imaging as an objective tool to monitor disease activity and to guide treatment decisions in patients with GCA (77,80,99,100,107–114). The results of these studies have highlighted a discrepancy between clinical and imaging assessment of large vessel vasculitis, as signals of vasculitis on imaging have been found in patients in apparent clinical remission, using magnetic resonance angiography (MRA) (99,100,107), PET (77,99,108–110,112,114), or ultrasound (80,111,115). Whether these signals represent subclinical vasculitis, atherosclerosis, tissue repair or vascular

remodelling is currently not well understood, due to the lack of histopathological comparisons (84,100).

It remains uncertain whether imaging may be helpful to predict future outcomes (20). Only few studies investigated whether patients in clinical remission but with signs of active vasculitis on PET are at a higher risk for future relapse during ongoing treatment (77,108,109). Grayson et al. assessed individuals with GCA and Takayasu's arteritis (TAK) who underwent a PET/CT scan while being in clinical remission and on mean daily glucocorticoid doses ≤5 mg. A summary score calculated from nine arterial segments was developed to assess the overall FDG uptake in each patient (PET vascular activity score; 'PETVAS'). During a median follow-up of 15 months, eight patients (20.5%) relapsed, with a higher likelihood of future clinical relapse observed among those with a high PETVAS (108). In contrast, in the study by Galli et al., PETVAS was not associated with subsequent relapse in retrospectively selected patients with GCA or TAK (109). One prospective study by Blockmans et al. evaluated the value of PET in predicting relapse in patients with GCA during and after treatment. PET was performed at diagnosis and 3 and 6 months thereafter. Eighteen patients (51.4%) relapsed a mean of 13.6 months after treatment start. A total vascular score calculated from 7 different vascular regions did not differentiate between patients who relapsed and those who remained in remission, regardless of the time of the PET scan (77). Given these controversial results and limited data, imaging is currently not routinely recommended for monitoring patients in clinical and biochemical remission (20,116).

To date, no reliable biomarkers are available for the prediction of disease progression after treatment discontinuation in patients with GCA (84). Consequently, the decision on when to safely discontinue glucocorticoid treatment is primarily based on symptoms, clinical findings and levels of acute-phase reactants (23). Whether imaging can guide the decision of when to discontinue treatment in patients with GCA remains unclear, as previous studies have

performed imaging at different stages of the disease rather than systematically at the end of treatment (77,108,109).

2 Aims of the thesis

The overall aim of this PhD thesis was to address the aforementioned research gaps in the epidemiology, management, and outcome of large vessel vasculitis in PMR and GCA, with the following specific objectives:

1. **Manuscript I:**

   Based on the high prevalence of subclinical GCA identified in our systematic literature review, the first manuscript addressed the hypothesis that a proportion of patients with newly diagnosed GCA and a history of PMR may have already had subclinical GCA at the time of PMR manifestation. If glucocorticoid doses used for PMR are insufficient to fully control subclinical GCA, more advanced vascular involvement could be expected once GCA becomes clinically apparent in these patients. Therefore, the objective was to investigate if a history of PMR in patients with newly diagnosed GCA is associated with more advanced vascular involvement on ultrasound and more ischemic events.

2. **Manuscript II:**

   The second manuscript aimed to investigate the incidence of permanent vision loss in patients with GCA treated at our centre during the last 15 years. Secondly, as early diagnosis of GCA and prompt administration of glucocorticoids are essential to prevent ocular ischemia, we aimed to identify obstacles in the patient pathway that may have caused a delay in treatment initiation. Thirdly, we aimed to identify clinical risk factors for permanent vision loss and to investigate the association between vascular ultrasound findings and occurrence of vision loss.

3. **Manuscript III:**

The third manuscript aimed to identify which parameters on MRI correspond to vasculitis in patients with newly diagnosed LV-GCA by comparing MRI findings to PET/CT and/or ultrasound findings in individual vessel segments (axillary segment per side, and the thoracic aorta).

4. **Manuscript IV:**

The fourth and final manuscript addressed the role of imaging performed at the end of treatment in its ability to predict the disease course of patients with LV-GCA after treatment discontinuation. The primary objective was to explore quantitative and qualitative vessel wall parameters detected by MRI and/or PET/CT for their ability to predict a relapse within 4 months after treatment discontinuation in patients with LV-GCA. The secondary objective was to identify if changes in imaging findings from diagnosis to treatment discontinuation were associated with GCA relapse within the first 4 months after treatment discontinuation.

3 Contributions by the PhD candidate

Manuscript I:

The first manuscript is based on our local cohort of patients with suspected GCA who underwent an ultrasound examination between December 2006 and May 2021. In collaboration with Markus Aschwanden, Stephan Imfeld, Thomas Daikeler, and medical master students, I contributed to the retrospective chart review and the electronic data entry of the 740 patients included in the cohort. Markus Aschwanden retrospectively read all stored ultrasound images of the 740 patients (more than 10,000 arterial segments). I contributed to the conception, design, and ethical approval of the study, performed the statistical analyses, and drafted the manuscript. In weekly meetings with my co-authors, we discussed and interpreted the results. According to the author guidelines, I submitted the manuscript and revised it in line with the comments raised by the reviewers with the support of my co-authors.

Manuscript II:

This manuscript was published with equal contributions from Thomas Daikeler, Markus Aschwanden, Stephan Imfeld and myself and was based on the beforementioned cohort of patients suspected of GCA. With my supervisor and collaborators from the Department of Angiology, we designed the study and formulated the research question. I retrospectively reviewed the medical records of all included patients to additionally incorporate data on ophthalmic examination results, place, and date of first consultation, reason for medical examination, and date of glucocorticoid treatment initiation into our database (total of 311 patients). I performed the data analyses, wrote the manuscript draft and was responsible for the submission process, revision of the paper and publication process. Thomas Daikeler and Stephan Imfeld were significantly involved in the interpretation of the data, helped with the statistical analyses, and writing of the manuscript.

Manuscript III:

The third manuscript was published with equal contributions from Thomas Daikeler, Gregor Sommer, Christof Rottenburger and myself and included patients from our prospective cohort study (Manuscript IV) and local GCA cohort ('Basler Riesenzellarteriitis Kohorte' – BARK). With my supervisor and collaborators from the Department of Radiology and Division of Nuclear Medicine, we designed the study and formulated the research question. I was involved in patient recruitment, retrospective medical chart review, and electronic data entry. Gregor Sommer and Christof Rottenburger read the MRI and PET/CT scans, respectively. Markus Aschwanden re-assessed all ultrasound images. I drafted the manuscript, discussed and interpreted the results with all co-authors and was responsible for the submission process. Thomas Daikeler substantially contributed to the writing of the manuscript.

Manuscript IV:

The fourth manuscript was a mixed prospective and retrospective cohort study. My first supervisor designed the study, formulated the research question and was responsible for ethical approval in collaboration with Gregor Sommer and Christof Rottenburger. During my PhD, I was involved in patient recruitment, retrospective medical chart review, and electronic data entry in collaboration with a medical master student. Gregor Sommer and Christof Rottenburger read the MRI and PET/CT scans, respectively. I performed the statistical analyses of the data, and discussed and interpreted the results with the co-authors. I drafted the manuscript and was responsible for the submission process with the support of my first supervisor and co-authors.

Other contributions:

In addition to the aforementioned publications, I had the opportunity to contribute as first or co-author to several projects in the field of my PhD, both in our GCA/PMR group at the University Hospital Basel as well as in national and international collaborations (49,117–121).

In the frame of our local GCA/PMR group, I was shared first author of a systematic literature review and individual patient meta-analysis on the prevalence and characteristics of subclinical GCA in PMR which provided the basis for this PhD thesis (49). I was the first author of a study which evaluated the diagnostic performance of the new ACR/EULAR classification criteria for GCA in our local GCA cohort, which was published as a letter in 'Arthritis & Rheumatology', one of the top journals in rheumatology (120). Furthermore, I was a co-author of a study which investigated the feasibility of a rapid glucocorticoid tapering regimen in patients with GCA (121) and contributed to the conception and protocol writing of a study on predictive factors for treatment response in patients with newly diagnosed PMR and GCA, which investigates interindividual responses to glucocorticoid treatment (NCT05479448). I had the opportunity to present the results of some of these studies as posters at various congresses (EULAR congress 2021 (122), ACR Convergence 2022 (123), EULAR congress 2023 (124)) and as an oral presentation at the Clinical Research Day 2023 at the University Basel ('Long delay from symptom onset to first consultation contributes to vision loss in patients with GCA').

I was involved in the development of a national survey which was distributed among specialists in Switzerland caring for patients with GCA to assess current practices in diagnosing, treating, and following-up GCA (117). Additionally, I participated in an international study investigating current management practices for PMR by general practitioners and rheumatologists and helped to organise the distribution of the questionnaire in Switzerland (118). I was a fellow of the 'International PMR Referrals Recommendation Group', which is a subgroup of the international GCA and PMR study group, with the goal of providing the current evidence towards early referral and management strategies in patients suspected of PMR. Together with another PhD student, I conducted the systematic literature review of early referral practices for patients with PMR (119). The findings of this systematic review will contribute to the development of evidence-based recommendations in forthcoming recommendations by the 'PMR Referrals Recommendation Group' (manuscript in preparation).

In 2020, a national prospective cohort for PMR and GCA patients in the frame of the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) was established, which allows detailed and longitudinal documentation of patients' clinical findings, lab results, imaging and treatment. I was involved in the establishment of the cohort at the University of Basel, in patient recruitment, in the promotion of the SCQM cohort in Swiss centres, and in drafting the protocol for a cohort profile. Finally, I was involved in supervising three medical students on their Master theses and one MD student on her dissertation.

4 Manuscripts

4.1 Manuscript I: Prior polymyalgia rheumatica is associated with sonographic vasculitic changes in newly diagnosed patients with giant cell arteritis

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Key words: Giant cell arteritis, polymyalgia rheumatica, ultrasound, vasculitis, subclinical vasculitis, vascular stenosis.

Abstract

Objectives: To investigate the hypothesis that a history of polymyalgia rheumatica (PMR) is associated with a more severe and damaging disease course in newly diagnosed giant cell arteritis (GCA) patients.

Methods: Retrospective analysis of GCA patients diagnosed between 12/2006 and 05/2021. We compared vascular ultrasound findings (presence of vasculitis and vascular stenosis) in GCA patients with and without prior PMR.

Results: 49 of 311 GCA patients (15.8%) had prior PMR in median 30.6 (IQR 7.1-67.3) months before GCA diagnosis. Patients with prior PMR had more often large vessel vasculitis (LVV) (51.0% vs. 25.0%, $p<0.001$) and stenosis within the vasculitic segments (18.4% vs. 3.1%, $p<0.001$) on ultrasound. In multivariable analysis, prior PMR remained significantly associated with LVV (OR 7.65, 95% CI 2.72–23.97, $p<0.001$). Polymyalgic symptoms at GCA diagnosis in the patients without prior PMR were not associated with a higher prevalence of LVV ($p=0.156$).

Conclusion: Patients with a diagnosis of PMR before GCA diagnosis had two times more often large vessel involvement and significant more vasculitic stenoses on ultrasound examination than patients without prior PMR. Pre-existing PMR is an independent risk factor for more extensive and advanced ultrasound findings at GCA diagnosis. The contribution of subclinical vasculitis to disease associated damage has to be further studied.

Key messages

- Patients with newly diagnosed GCA with a history of PMR have more often ultrasonographic large-vessel involvement and vasculitic stenosis at GCA diagnosis compared to patients without prior PMR.
- PMR patients should be screened for subclinical vasculitis independent of the clinical presentation.

Introduction

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are related inflammatory rheumatic diseases which frequently overlap. They may be diagnosed together or at different time-points. PMR may precede GCA up to years (1). In a number of cases, symptoms of PMR may be the only clinical manifestation of GCA (2). Such subclinical GCA in clinically isolated PMR can be found in 29% of patients if systematically screened for by positron emission tomography (3) and in 22% if screened for by ultrasound (4). Standard glucocorticoid doses used for PMR treatment relieve PMR symptoms but may be insufficient to completely suppress subclinical vasculitis. Despite normalised inflammation markers during treatment of PMR patients, vasculitis may progress even in asymptomatic patients (1,5). Thus, when GCA eventually becomes clinically apparent and is diagnosed in patients with PMR, those with prior subclinical GCA may present with more advanced vessel wall thickening and more advanced vasculitic stenosis.

To investigate the hypothesis that prior PMR is associated with a more severe and damaging disease course in patients with newly diagnosed GCA, this study compared vascular ultrasound findings in newly diagnosed GCA patients with and without prior PMR.

Methods

Patients and setting

This retrospective analysis includes all GCA patients diagnosed between December 2006 and May 2021 at the University Hospital of Basel. All patients underwent routine vascular ultrasound of the supra-aortic vessels for diagnostic work-up as previously described (6). This study was approved by the local Ethics committee (EKNZ, Project-ID 2021-00681). Due to the retrospective nature of the study, participants were not required to provide written consent according to Human Research Act art. 34/Human Research Ordinance.

Data collection

Patient data were obtained from the local Basel GCA cohort ('BARK') and from retrospective chart review (7). We recorded patient demographics, clinical manifestations, laboratory and imaging findings at the time of GCA diagnosis and assessed whether a previous diagnosis of PMR had preceded the diagnosis of GCA. GCA was diagnosed if temporal artery biopsy was positive, if the 1990 criteria from the American College of Rheumatology (ACR) were met or at least 2/5 ACR criteria were fulfilled in combination with findings typical for vasculitis in imaging.

Ultrasound

For ultrasound examinations, iU22 ultrasound devices with a linear 9-3 MHz and 17-5 MHz transducer or EPIQ 7 duplex devices with a linear 12-3 MHz and 18-5 MHz transducer (both from Philips, Best, The Netherlands) were used (8). An experienced angiologist (MA) reread and verified all ultrasound image classifications within the cohort. The following arteries were bilaterally categorised as 'normal', 'vasculitis', or 'arteriosclerosis': the large vessels (i.e., the common, internal, and external carotid arteries, the vertebral, subclavian and axillary arteries), and the superficial temporal arteries (trunk, parietal, and frontal branch). Vasculitis in the temporal artery was detected using the compression sign (9). For larger vessels, vasculitis was defined as circumferential homogenous hypoechoic wall thickening, well-delineated towards the luminal side and without arteriosclerotic lesions (7).

'Arteriosclerosis' on ultrasound examination was defined as irregularly delineated, non-homogenous eccentric or calcified vessel wall alterations (7). A patient was defined as having arteriosclerosis if at least one vessel segment was classified as 'arteriosclerosis'.

Vascular stenoses were assessed in the axillary, vertebral and internal carotid arteries that were categorised as 'vasculitis' on ultrasound and were defined as narrowing of the vessel lumen of ≥50% in diameter ('vasculitic stenosis').

Vessel regions were analysed by combining the ultrasound results of the two sides of the body as follows: if at least one vessel segment at one of the two sides was judged as vasculitis in ultrasound, the region was defined as vasculitic.

Large vessel vasculitis (LVV) was defined as ultrasound findings consistent with vasculitis in any of the examined vessels except the temporal artery (i.e., vasculitis in the carotid, vertebral, subclavian and/or axillary arteries).

Statistical analysis

Continuous variables are expressed as medians with interquartile ranges (IQR). Categorical variables are presented as numbers with percentages. Quantitative differences between groups were analysed using the Student's t-test or the Mann-Whitney U test, as appropriate. Categorical variables were compared using the chi-square or Fisher's exact test. We applied the Holm-Bonferroni correction to control for multiple testing (10). A p-value of <0.05 was considered statistically significant. Logistic regression analysis was used to examine the association between a history of PMR and presence of LVV (yes/no) in the carotid, vertebral, subclavian and/or axillary arteries and presence of vasculitic stenosis (yes/no) in the internal carotid, vertebral and/or axillary artery segments on ultrasound. Odds ratios (OR) and 95% confidence intervals (CI) were computed for each variable in univariable analyses and in multivariable analyses using the bi-directional stepwise approach, including all variables from univariable analysis. Multicollinearity was assessed using the variance inflation factors. Subgroup analyses were conducted i) to compare ultrasonographic findings in the subgroup of patients with cranial GCA and ii) to evaluate whether polymyalgic symptoms at GCA diagnosis are associated with more extensive ultrasound findings in the subgroup of patients without a prior diagnosis of PMR. All statistical analyses were performed in RStudio version 2021.9.0.351 (2021-09-20) (11).

Results

Study cohort

We studied 311 patients diagnosed with GCA (63% females) with a median age of 73.8 years (IQR 67.6-78.8 years). Of those, 49 (15.8%) patients had a preceding diagnosis of PMR a median of 30.6 (IQR 7.1-67.3) months before GCA diagnosis. Of these, 27/49 (55.1%) did not take any glucocorticoids at the time of GCA diagnosis. The remaining 22 patients (44.9%) were taking a median of 9.5 mg (IQR 5.0–18.8 mg) of glucocorticoids at the time they presented for suspected GCA. Clinical LVV was diagnosed in 29.1% and cranial GCA in 74.3%. At GCA diagnosis, patients who had prior PMR reported less frequently cranial symptoms such as headache, jaw claudication or scalp tenderness (60.4% vs. 77.1%, p=0.014) compared to patients without prior PMR. Furthermore, patients with prior PMR had less often arteriosclerotic findings on ultrasound examination (40.8% vs. 61.5%, p=0.007) and a lower median erythrocyte sedimentation rate (50.0 mm/h [IQR 28.0–72.0] vs. 72.0 mm/h [IQR 41.5–90.0], p=0.002) (Table 1).

Vasculitis on ultrasound

Of all arterial segments assessed (311x18=5598), 5417 (96.8%) could be analysed and 181 (3.2%) had missing values (e.g., due to temporal artery biopsy in this segment or due to poor image quality).

Patients with prior PMR were two times more likely to have LVV on ultrasound (51%) compared to patients without prior PMR (25%, p<0.001) whereas there was no such difference in the temporal artery segments (63.3% vs. 61.7%, p=0.838) (Table 1, Supplementary Table S1).

Multivariable analysis of patients' symptoms, medical history, clinical and laboratory findings revealed prior PMR as statistically significantly associated with ultrasound findings typical for LVV (OR 7.65, 95% CI 2.72–23.97, p<0.001) (Table 2).

LVV was also more prevalent in patients with prior PMR when the subgroup of patients with cranial GCA was analysed (44.8% vs. 21.5%, p=0.006) (Supplementary Tables S3-S4).

In the subgroup of patients without prior PMR, patients with and without polymyalgic symptoms at GCA diagnosis did not differ in the prevalence of LVV (29% vs 21.1%, p=0.156, Supplementary Tables S5-S6).

Vasculitic stenoses on ultrasound

Overall, 17/311 (5.5%) patients were found to have vasculitic stenosis in at least one segment of the large arteries. A total of 9/49 (18.4%) patients with prior PMR had large-vessel stenosis compared with 8/262 (3.1%) patients without prior PMR (p<0.001). This was most pronounced in the vertebral arteries, with stenoses in 5/49 (10.2%) of patients with prior PMR compared with 2/262 (0.8%) in patients without prior PMR (p=0.004) (Table 1).

Overall, a history of PMR was significantly associated with stenosis on ultrasound in univariable logistic regression analysis (OR 3.82, 95% CI 1.26–11.95, p=0.018) (Supplementary Table S2). In the subgroup of patients with cranial GCA, stenoses remained more frequent in those with prior PMR (13.8% vs. 1.5%, p=0.005) (Supplementary Table S7). In patients without prior PMR, there was no statistically significant difference in the prevalence of stenoses between patients with and without polymyalgic symptoms at GCA diagnosis (5.3% vs. 1.3%, p=0.109) (Supplementary Table S8).

Stroke at GCA diagnosis

Of all 311 patients, 14 (4.5%) patients suffered from stroke at GCA diagnosis; 4/49 (8.2%) patients with prior PMR and 10/262 (3.8%) without prior PMR (p=0.249).

Patients with stroke had significantly more often vertebral artery stenoses compared with patients without stroke (4/14 [28.6%] vs. 3/297 [1.0%], p<0.001, Supplementary Table S9). In these four patients with stroke and vasculitic vertebral artery stenosis, ischemic events occurred in the area supplied by the vertebral arteries.

Discussion

In our cohort, 15% of newly diagnosed GCA patients had a preceding diagnosis of PMR, this is in the range of previous retrospective studies (1,5). We found that patients with prior PMR had significantly more often LVV compared to patients without prior PMR. LVV is the most prevalent phenotype of subclinical GCA if PMR patients were systematically screened at diagnosis (3,12). This suggests that a substantial proportion of these newly diagnosed GCA patients indeed suffered not only from prior PMR but also from undiagnosed prior subclinical GCA.

The finding that patients with prior PMR had a higher frequency of vasculitic stenoses compared to those without prior PMR further supports the hypothesis of an inadequately treated pre-existing subclinical GCA. Of note, the presence of stenoses was not related to arteriosclerotic disease manifestations. In the patients with prior PMR, vasculitic stenoses were most frequently found in the vertebral arteries. Vertebral artery stenoses in GCA are clinically relevant and have been shown to be associated with stroke (13). Indeed, we found that in four patients of our cohort, cerebral ischemia was associated with the presence of vasculitic vertebral stenosis. Although the significantly higher rate of vertebral artery stenosis in patients with prior PMR in our cohort may put these patients at a higher risk of cerebrovascular events, we did not find direct evidence for an association between prior PMR and stroke, likely due to a low event rate.

Taken together, our data support the concept of non-diagnosed subclinical vasculitis in patients with PMR contributing to advanced vessel wall pathologies at subsequent GCA diagnosis. This is further supported by the finding that only a history of prior PMR but not the presence of polymyalgic symptoms at GCA diagnosis was associated with more extensive ultrasound findings.

Vasculitic stenoses are a risk factor for stroke and other ischemic complications, therefore screening of PMR patients for subclinical GCA may allow to adequately adapt therapy beforehand. Controlled prospective studies are needed to confirm our hypothesis.

The major limitation of our study is the retrospective design. We cannot exclude that we may have missed some patients with prior PMR. However, since we systematically assessed the patients' history for signs of GCA or PMR, it is unlikely that this number is substantial. We have no information on the treatment of prior PMR and therefore can only assume that treatment was insufficient to control potential underlying subclinical vasculitis. We did not assess smaller quantitative differences, e.g. by measuring the intima-media thickness (14). Future studies are needed to allow quantitative comparison of intima-media thickness values between patients with and without prior PMR. Furthermore, whether these patients had indeed subclinical LV-GCA before their GCA diagnosis cannot be answered from our data.

Conclusion

Patients with GCA having a history of PMR present a subset of patients at higher risk for LVV and vasculitic stenoses at GCA diagnosis compared to patients without prior PMR. The more advanced vasculitic vessel wall pathologies of these patients suggest that subclinical GCA may have been present before GCA diagnosis. Treatment for PMR may be insufficient to completely control subclinical vasculitis. Our data support the need for screening strategies for subclinical GCA in patients with PMR.

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Conflict of interest

AH is supported by a grant from the Swiss Foundation for Research on Muscle Diseases (FSRMM). CTB received a grant from the Swiss National Science Foundation (SNSF). DK received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, Janssen, Novartis, Pfizer, Roche and Eli Lilly and support for attending meetings and/or travel from Janssen. All other authors have no competing interests.

Contributors

All authors gave substantial contributions to study conception or design of the work, acquisition of data, analysis or interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version of the article to be published.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Data availability

The data used and analysed during this study are available from the corresponding author upon reasonable request.

Ethics

This study was approved by the local Ethics committee (EKNZ, Project-ID 2021-00681).

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Table legends

Table 1: Characteristics of GCA patients with and without a prior history of PMR.

Table 2: Logistic regression showing the association between patient characteristics and large-vessel vasculitis on ultrasound (yes/no).

Table 1: Characteristics of GCA patients with and without a prior history of PMR.			
	GCA without prior PMR (N=262)	**GCA with prior PMR (N=49)**	**p-value**
Patient characteristics			
Age, years	73.5 (67.3-79.2); N=262	74.4 (70.0-78.0); N=49	0.633
Female	166/262 (63.4)	30/49 (61.2)	0.776
Hypertension	128/255 (50.2)	28/48 (58.3)	0.301
Diabetes	49/256 (19.1)	8/47 (17.0)	0.733
Dyslipidemia	64/251 (25.5)	14/47 (29.8)	0.539
Smoking	91/246 (37.0)	10/47 (21.3)	0.038
Arteriosclerosis on ultrasound	160/260 (61.5)	20/49 (40.8)	0.007
History of coronary artery disease	39/250 (15.6)	5/48 (10.4)	0.354
History of cerebrovascular disease	22/251 (8.8)	7/48 (14.6)	0.282
Peripheral artery disease	20/250 (8.0)	8/48 (16.7)	0.099
ESR, mm/h	72 (41.5-90.0); N=240	50.0 (28.0-72.0); N=45	0.002
CRP, mg/dl	57.6 (25.6-110.3); N=259	52.8 (17.3-102.5); N=48	0.336
Leukocytes, G/l	9.8 (7.9-11.6); N=246	10.4 (8.3-12.3); N=44	0.287
Fever	39/245 (15.9)	3/45 (6.7)	0.105
Headache	164/256 (64.1)	24/47 (51.1)	0.091
Jaw claudication	110/256 (43.0)	16/46 (34.8)	0.3
Scalp tenderness	102/230 (44.3)	10/41 (24.4)	0.02
At least one cranial symptom[a]	202/262 (77.1)	29/48 (60.4)	0.014
Polymyalgic symptoms	94/247 (38.1)	25/47 (53.2)	0.053
Tenderness of the temporal artery	82/216 (38.0)	13/39 (33.3)	0.582
Stroke	10/262 (3.8)	4/49 (8.2)	0.249
Permanent vision loss	38/262 (14.5)	7/49 (14.3)	0.968
Vasculitis			
Temporal arteries	158/256 (61.7)	31/49 (63.3)	0.838
Overall large vessel involvement[b]	65/260 (25.0)	25/49 (51.0)	<0.001
Carotid arteries	12/258 (4.7)	6/49 (12.2)	0.088[c]
Vertebral arteries	30/255 (11.8)	11/49 (22.4)	0.088[c]
Subclavian arteries	27/260 (10.4)	12/49 (24.5)	0.024[c]
Axillary arteries	36/254 (14.2)	14/49 (28.6)	0.039[c]
Vasculitic stenosis			
Overall[d]	8/262 (3.1)	9/49 (18.4)	<0.001
Internal carotid artery	0/262 (0.0)	1/49 (2.0)	0.158[c]
Vertebral artery	2/262 (0.8)	5/49 (10.2)	0.004[c]
Axillary artery	7/262 (2.7)	4/49 (8.2)	0.154[c]

Abbreviations: GCA: giant cell arteritis; PMR: polymyalgia rheumatica.

Categorical variables are shown as n/N (%) and continuous variables as medians with interquartile ranges.

[a]Presence of headache, jaw claudication and/or scalp tenderness.

[b]Vascular involvement in at least one large-vessel segment (carotid, vertebral, subclavian and/or axillary arteries).

[c]*p*-values are corrected for multiple testing with the Holm-Bonferroni method.

[d]Number of patients with vascular stenosis in at least one arterial segment.

Table 2: Logistic regression showing the association between patient characteristics and large-vessel vasculitis on ultrasound (yes/no).

	Univariable analysis			Multivariable analysis		
Independent variables	**Odds ratio**	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
History of PMR	3.12	1.67 – 5.88	<0.001	7.65	2.72 – 23.97	<0.001
Age, years	1	0.97 – 1.03	0.822	-	-	-
Female	1.78	1.05 – 3.08	0.034	2.08	0.92 – 4.95	0.087
Hypertension	0.83	0.51 – 1.37	0.475	-	-	-
Diabetes	1.1	0.58 – 2.03	0.759	-	-	-
Dyslipidemia	0.99	0.55 – 1.73	0.965	-	-	-
Smoking	1.14	0.68 – 1.91	0.618	-	-	-
Coronary artery disease	0.67	0.30 – 1.38	0.295	-	-	-
Cerebrovascular disease	0.91	0.37 – 2.07	0.832	0.30	0.05 – 1.28	0.137
Peripheral artery disease	0.63	0.23 – 1.52	0.335	0.21	0.03 – 1.03	0.084
ESR, mm/h	1	0.99 – 1.01	0.749	-	-	-
CRP, mg/dl	1	0.99 – 1.00	0.081	0.99	0.99 – 1.00	0.104
Leukocytes, G/l	0.95	0.87 – 1.03	0.242	-	-	-
Fever	0.63	0.27 – 1.34	0.256	-	-	-
Headache	0.57	0.34 – 0.95	0.03	0.50	0.23 – 1.10	0.084
Jaw claudication	0.88	0.53 – 1.47	0.635	-	-	-
Scalp tenderness	0.41	0.23 – 0.72	0.002	-	-	-
Polymyalgia symptoms	1.23	0.74 – 2.06	0.421	-	-	-
Tenderness of the temporal artery	0.5	0.27 – 0.91	0.026	0.34	0.13 – 0.82	0.021

Abbreviations: CI: confidence interval; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GCA: giant cell arteritis; PMR: polymyalgia rheumatica.
Large-vessel vasculitis was defined as the involvement of the carotid, vertebral, subclavian and/or axillary arteries. A bi-directional stepwise approach was used.

Supplementary Material

Supplementary Table S1: Number of patients with vessels categorized as vasculitis on ultrasound.

Vascular segment	All (n=311)	GCA without prior PMR (n=262)	GCA with prior PMR (n=49)
Internal carotid artery, right			
No vasculitis	302 (97.1)	254 (96.9)	48 (98.0)
Vasculitis	3 (1.0)	3 (1.1)	0 (0.0)
NA	6 (1.9)	5 (1.9)	1 (2.0)
Internal carotid artery, left			
No vasculitis	301 (96.8)	253 (96.6)	48 (98.0)
Vasculitis	3 (1.0)	2 (0.8)	1 (2.0)
NA	7 (2.3)	7 (2.7)	0 (0.0)
External carotid artery, right			
No vasculitis	288 (92.6)	243 (92.7)	45 (91.8)
Vasculitis	12 (3.9)	8 (3.1)	4 (8.2)
NA	11 (3.5)	11 (4.2)	0 (0.0)
External carotid artery, left			
No vasculitis	296 (95.2)	249 (95.0)	47 (95.9)
Vasculitis	4 (1.3)	2 (0.8)	2 (4.1)
NA	11 (3.5)	11 (4.2)	0 (0.0)
Common carotid artery, right			
No vasculitis	301 (96.8)	254 (96.9)	47 (95.9)
Vasculitis	6 (1.9)	4 (1.5)	2 (4.1)
NA	4 (1.3)	4 (1.5)	0 (0.0)
Common carotid artery, left			
No vasculitis	302 (97.1)	255 (97.3)	47 (95.9)
Vasculitis	5 (1.6)	3 (1.1)	2 (4.1)
NA	4 (1.3)	4 (1.5)	0 (0.0)
Vertebral artery, right			
No vasculitis	273 (87.8)	232 (88.5)	41 (83.7)
Vasculitis	29 (9.3)	21 (8.0)	8 (16.3)
NA	9 (2.9)	9 (3.4)	0 (0.0)
Vertebral artery, left			
No vasculitis	268 (86.2)	227 (86.6)	41 (83.7)
Vasculitis	31 (10.0)	23 (8.8)	8 (16.3)
NA	12 (3.9)	12 (4.6)	0 (0.0)
Subclavian artery, right			
No vasculitis	274 (88.1)	236 (90.1)	38 (77.6)
Vasculitis	30 (9.6)	20 (7.6)	10 (20.4)
NA	7 (2.3)	6 (2.3)	1 (2.0)
Subclavian artery, left			

No vasculitis	274 (88.1)	235 (89.7)	39 (79.6)
Vasculitis	34 (10.9)	24 (9.2)	10 (20.4)
NA	3 (1.0)	3 (1.1)	0 (0.0)
Axillary artery, right			
No vasculitis	258 (83.0)	223 (85.1)	35 (71.4)
Vasculitis	41 (13.2)	28 (10.7)	13 (26.5)
NA	12 (3.9)	11 (4.2)	1 (2.0)
Axillary artery, left			
No vasculitis	257 (82.6)	222 (84.7)	35 (71.4)
Vasculitis	43 (13.8)	30 (11.5)	13 (26.5)
NA	11 (3.5)	10 (3.8)	1 (2.0)
Superficial temporal artery, all, right			
No vasculitis	125 (40.2)	106 (40.5)	19 (38.8)
Vasculitis	179 (57.6)	149 (56.9)	30 (61.2)
NA	7 (2.3)	7 (2.7)	0 (0.0)
Superficial temporal artery, all, left			
No vasculitis	147 (47.3)	124 (47.3)	23 (46.9)
Vasculitis	157 (50.5)	131 (50.0)	26 (53.1)
NA	7 (2.3)	7 (2.7)	0 (0.0)
Superficial temporal artery, trunk, right			
No vasculitis	168 (54.0)	142 (54.2)	26 (53.1)
Vasculitis	132 (42.4)	109 (41.6)	23 (46.9)
NA	11 (3.5)	11 (4.2)	0 (0.0)
Superficial temporal artery, trunk, left			
No vasculitis	185 (59.5)	154 (58.8)	31 (63.3)
Vasculitis	110 (35.4)	94 (35.9)	16 (32.7)
NA	16 (5.1)	14 (5.3)	2 (4.1)
Superficial temporal artery, frontal branch, right			
No vasculitis	159 (51.1)	131 (50.0)	28 (57.1)
Vasculitis	141 (45.3)	121 (46.2)	20 (40.8)
NA	11 (3.5)	10 (3.8)	1 (2.0)
Superficial temporal artery, frontal branch, left			
No vasculitis	168 (54.0)	142 (54.2)	26 (53.1)
Vasculitis	132 (42.4)	109 (41.6)	23 (46.9)
NA	11 (3.5)	11 (4.2)	0 (0.0)
Superficial temporal artery, parietal branch, right			
No vasculitis	192 (61.7)	162 (61.8)	30 (61.2)
Vasculitis	100 (32.2)	85 (32.4)	15 (30.6)
NA	19 (6.1)	15 (5.7)	4 (8.2)
Superficial temporal artery, parietal branch, left			
No vasculitis	197 (63.3)	166 (63.4)	31 (63.3)
Vasculitis	98 (31.5)	82 (31.3)	16 (32.7)

NA	16 (5.1)	14 (5.3)	2 (4.1)
Abbreviations: GCA: giant cell arteritis; NA: not available; PMR: polymyalgia rheumatica. Variables are presented as frequencies and proportion.			

Supplementary Table S2: Univariable logistic regression showing the association between patient characteristics and the presence of vasculitic stenoses (yes/no) in the large vessels (internal carotid, vertebral and axillary arterial segment).

	Univariable analysis		
Independent variables	**Odds ratio**	**95% CI**	**p-value**
History of PMR	3.82	1.26 – 11.95	0.018
Age, years	0.96	0.90 – 1.03	0.289
Female	2.03	0.58 – 9.50	0.305
Hypertension	1.13	0.37 – 3.42	0.828
Diabetes	1.7	0.47 – 5.52	0.389
Dyslipidemia	1.39	0.39 – 4.43	0.589
Smoking	0.44	0.12 – 1.41	0.194
Arteriosclerosis on ultrasound	0.89	0.29 – 2.61	0.838
Coronary artery disease	0.47	0.02 – 2.84	0.488
Cerebrovascular disease	1.69	0.23 – 8.76	0.556
Peripheral artery disease	0.79	0.04 – 5.38	0.832
ESR, mm/h	0.97	0.94 – 0.99	0.007
CRP, mg/dl	0.99	0.97 – 1.00	0.094
Leukocytes, G/l	1.12	0.90 – 1.39	0.308
Fever	1.19	0.16 – 5.63	0.842
Headache	0.3	0.09 – 0.94	0.045
Jaw claudication	0.69	0.19 – 2.16	0.531
Scalp tenderness	0.14	0.01 – 0.75	0.062
Polymyalgia symptoms	1.62	0.54 – 5.07	0.395
Tenderness of the temporal artery	0.68	0.14 – 2.53	0.589
Abbreviations: CI: confidence interval; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GCA: giant cell arteritis; PMR: polymyalgia rheumatica.			

Supplementary Table S3: Subgroup analysis of patients with cranial GCA. Number of patients with arterial segments categorized as vasculitis on ultrasound.

Arterial segment categorized as vasculitis	No prior PMR (N=202)	Prior PMR (N=29)	p-value
Temporal arteries	131/199 (65.8)	20/29 (69.0)	0.739
Overall large vessel involvement[a]	43/200 (21.5)	13/29 (44.8)	0.006
Carotid arteries	6/199 (3.0)	2/29 (6.9)	1.0[b]
Vertebral arteries	20/198 (10.1)	9/29 (31.0)	0.031[b]
Subclavian arteries	15/100 (7.5)	4/29 (13.8)	1.0[b]
Axillary arteries	21/197 (10.7)	4/29 (13.8)	1.0[b]

Abbreviations: PMR: polymyalgia rheumatica. Variables are shown as n/N (%).
[a]Vascular involvement in at least one large-vessel segment (carotid, vertebral, subclavian and/or axillary arteries).
[b]*p*-values are corrected for multiple testing with the Holm-Bonferroni method.

Supplementary Table S4: Subgroup analysis of patients with cranial GCA. Univariable and multivariable (bi-directional stepwise approach) logistic regression showing the association between patient characteristics and large-vessel vasculitis on ultrasound (yes/no) (carotid, vertebral, subclavian and/or axillary arteries) in patients with cranial giant cell arteritis.

	Univariable analysis			Multivariable analysis		
Independent variables	**Odds ratio**	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
History of PMR	2.97	1.31 – 6.64	0.008	19.8	4.28 – 119.92	<0.001
Age, years	1.01	0.97 – 1.04	0.678	-	-	-
Female	2.19	1.13 – 4.52	0.026	-	-	-
Hypertension	0.8	0.43 – 1.48	0.482	-	-	-
Diabetes	1.07	0.48 – 2.26	0.858	-	-	-
Dyslipidemia	0.77	0.35 – 1.59	0.497	0.21	0.03 – 1.07	0.088
Smoking	1.47	0.79 – 2.74	0.223	-	-	-
Coronary artery disease	0.99	0.37 – 2.36	0.981	4.4	0.62 – 33.59	0.137
Cerebrovascular disease	1.63	0.54 – 4.44	0.355	-	-	-
Peripheral artery disease	0.52	0.12 – 1.64	0.316	0.11	0.00 – 1.03	0.1
ESR, mm/h	1	0.99 – 1.01	0.796	1.03	1.01 – 1.05	0.013
CRP, mg/dl	1	0.99 – 1.00	0.141	0.98	0.97 – 1.00	0.018
Leukocytes, G/l	0.94	0.84 – 1.05	0.296	0.78	0.63 – 0.94	0.015
Fever	0.86	0.32 – 2.03	0.742	-	-	-
Headache	1.1	0.50 – 2.60	0.827	-	-	-
Jaw claudication	1.41	0.76 – 2.65	0.283	-	-	-
Scalp tenderness	0.54	0.28 – 1.04	0.068	-	-	-
Polymyalgic symptoms	1.89	1.01 – 3.58	0.047	-	-	-
Tenderness of the temporal artery	0.55	0.27 – 1.09	0.093	0.25	0.07 – 0.75	0.019

Abbreviations: CI: confidence interval; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GCA: giant cell arteritis; PMR: polymyalgia rheumatica.

Supplementary Table S5: Subgroup analysis of patients without prior PMR. Number of patients with arterial segments categorized as vasculitis on ultrasound in the subgroup of patients without prior PMR.

Arterial segment categorized as vasculitis	GCA without polymyalgic symptoms (N=153)	GCA with polymyalgic symptoms (N=94)	p-value
Temporal arteries	98/151 (64.9)	51/91 (56.0)	0.17
Overall large vessel involvement[a]	32/152 (21.1)	27/94 (29.0)	0.156
Carotid arteries	8/152 (5.3)	4/92 (4.3)	1.0[b]
Vertebral arteries	12/150 (7.9)	15/91 (16.5)	0.172[b]
Subclavian arteries	12/152 (7.9)	12/93 (12.9)	0.602[b]
Axillary arteries	19/147 (12.9)	13/93 (14.0)	1.0[b]

Abbreviations: PMR: polymyalgia rheumatica. Variables are shown as n/N (%).

[a]Vascular involvement in at least one large-vessel segment (carotid, vertebral, subclavian and/or axillary arteries).

[b]*p*-values are corrected for multiple testing with the Holm-Bonferroni method.

Supplementary Table S6: Subgroup analysis of patients without prior PMR. Univariable and multivariable (bi-directional stepwise approach) logistic regression showing the association between patient characteristics and large-vessel vasculitis on ultrasound (yes/no) (carotid, vertebral, subclavian and/or axillary arteries) in patients with giant cell arteritis without a prior history of PMR.

	Univariable analysis			**Multivariable analysis**		
Independent variables	**Odds ratio**	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
Polymyalgic symptoms	1.53	0.84 – 2.78	0.158	-	-	-
Age, years	1.01	0.97 – 1.04	0.766	-	-	-
Female	2.27	1.19 – 4.56	0.016	-	-	-
Hypertension	0.59	0.32 – 1.08	0.091	-	-	-
Diabetes	0.78	0.33 – 1.68	0.54	0.28	0.04 – 1.10	0.108
Dyslipidemia	0.94	0.46 – 1.84	0.861	-	-	-
Smoking	1.27	0.69 – 2.32	0.433	-	-	-
Coronary artery disease	0.7	0.27 – 1.62	0.438	-	-	-
Cerebrovascular disease	0.54	0.12 – 1.68	0.339	-	-	-
Peripheral artery disease	0.18	0.01 – 0.93	0.105	-	-	-
ESR, mm/h	1	0.99 – 1.01	0.984	1.01	1.00 – 1.03	0.162
CRP, mg/dl	1	0.99 – 1.0	0.163	0.99	0.98 – 1.00	0.073
Leukocytes, G/l	0.95	0.86 – 1.06	0.38	-	-	-
Fever	0.72	0.28 – 1.67	0.475	-	-	-
Headache	0.73	0.4 – 1.33	0.299	-	-	-
Jaw claudication	0.87	0.47 – 1.57	0.637	-	-	-
Scalp tenderness	0.37	0.18 – 0.72	0.004	0.5	0.18 – 1.28	0.157
Tenderness of the temporal artery	0.48	0.23 – 0.96	0.044	0.39	0.13 – 1.05	0.075

Abbreviations: CI: confidence interval; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GCA: giant cell arteritis; PMR: polymyalgia rheumatica.

Supplementary Table S7: Subgroup analysis of patients with cranial GCA. Number of patients with vasculitic stenoses (≥50%) on ultrasound in the subgroup of patients with cranial GCA.

Arterial segment categorized as vasculitis on ultrasound	No prior PMR (N=202)	Prior PMR (N=29)	p-value
Overall[a]	3/202 (1.5)	4/29 (13.8)	0.005
Internal carotid artery	0/202 (0.0)	0/29 (0.0)	-
Vertebral artery	0/202 (0.0)	3/29 (10.3)	0.002[b]
Axillary artery	3/202 (1.5)	1/29 (3.4)	0.418[b]

Abbreviations: GCA: giant cell arteritis; PMR: polymyalgia rheumatica. Variables are shown as n/N (%).

[a]Number of patients with vascular stenosis in at least one arterial segment.

[b]*p*-values are corrected for multiple testing with the Holm-Bonferroni method.

Supplementary Table S8: Subgroup analysis of patients without prior PMR. Number of patients with vasculitic stenoses (≥50%) on ultrasound in the subgroup of patients without prior PMR.

Arterial segment categorized as vasculitis on ultrasound	GCA without polymyalgic symptoms (N=153)	GCA with polymyalgic symptoms (N=94)	p-value
Overall[a]	2/153 (1.3)	5/94 (5.3)	0.109
Internal carotid artery	0/153 (0.0)	0/94 (0.0)	-
Vertebral artery	1/153 (0.7)	0/94 (0.0)	1.0[b]
Axillary artery	1/153 (0.7)	5/94 (5.3)	0.062[b]

Abbreviations: GCA: giant cell arteritis; PMR: polymyalgia rheumatica. Variables are shown as n/N (%).

[a]Number of patients with vascular stenosis in at least one arterial segment.

[b]*p*-values are corrected for multiple testing with the Holm-Bonferroni method.

Supplementary Table S9: Characteristics of patients with and without stroke at GCA diagnosis.

Characteristics	No stroke (N=297)	Stroke (N=14)	p-value
Age, years	73.7 (67.4-78.5); N=297	77.1 (69.5-81.6); N=14	0.283
Female	189/297 (63.6)	7/14 (50.0)	0.302
History of PMR	45/297 (15.2)	4/14 (28.6)	0.249
Hypertension	146/289 (50.5)	10/14 (71.4)	0.126
Diabetes	49/289 (17.0)	8/14 (57.1)	0.001
Dyslipidemia	72/284 (25.4)	6/14 (42.9)	0.208
Smoking	95/279 (34.1)	6/14 (42.9)	0.568
Overall vascular stenosis*	13/297 (4.4)	4/14 (28.6)	0.004
Vertebral stenosis	3/297 (1.0)	4/14 (28.6)	<0.001
Arteriosclerosis	170/295 (57.6)	10/14 (71.4)	0.306
History of coronary artery disease	41/284 (14.4)	3/14 (21.4)	0.443
History of cerebrovascular disease	25/285 (8.8)	4/14 (28.6)	0.036
Peripheral artery disease	26/284 (9.2)	2/14 (14.3)	0.629
ESR, mm/h	70 (41.5-88.0); N=272	34.0 (20.0-60.0); N=13	0.004
CRP, mg/dl	59.4 (26.2-110.0); N=293	29.0 (10.0-41.5); N=14	0.013
Leukocytes, G/l	9.86 (8.1-11.7); N=276	9.3 (7.2-11.0); N=14	0.464
Fever	41/277 (14.8)	1/13 (7.7)	0.7
Headache	183/290 (63.1)	5/13 (38.5)	0.085
Jaw claudication	120/289 (41.5)	6/13 (46.2)	0.74
Scalp tenderness	110/258 (42.6)	2/13 (15.4)	0.051
Polymyalgic symptoms	111/281 (39.5)	8/13 (61.5)	0.114
Tenderness of the temporal artery	93/246 (37.8)	2/9 (22.2)	0.49
Permanent vision loss	45/297 (15.2)	0/14 (0.0)	0.235

Abbreviations: GCA: giant cell arteritis; PMR: polymyalgia rheumatica.

Categorical variables are shown as n/N (%) and continuous variables as medians with interquartile ranges.

*Vascular stenosis in at least one vasculitic segment (axillary, vertebral and/or carotid artery).

4.2 Manuscript II: Long delay from symptom onset to first consultation contributes to permanent vision loss in patients with giant cell arteritis: a cohort study

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Keywords: giant cell arteritis, permanent vision loss, fast-track clinic

Abstract

Objectives: To characterise factors associated with permanent vision loss (PVL) and potential reasons for the therapeutic delay contributing to PVL in giant cell arteritis (GCA).

Methods: Retrospective analysis of GCA patients diagnosed at the University Hospital Basel between December 2006 and May 2021.

Results: Of 282 patients with GCA (64% females), 49 (17.4%) experienced PVL. In 43/49 (87.8%) PVL occurred before treatment. Of these, 24 (55.8%) patients had first non-ocular symptoms and eventually sought consultation when PVL occurred in a median of 21 (IQR 14.75-31.0) days after the first symptoms. Only five of the 24 patients had consulted a physician before PVL, but GCA diagnosis was missed. Treatment was initiated rapidly after diagnosis (median 1 day [IQR 0.0-7.0]). PVL on therapy occurred in six patients in a median of 40 (IQR 20.5-67.3) days after treatment started. In two of those, glucocorticoids were tapered too quickly.

In multivariable analysis, patients with PVL were older (OR 1.17, 95% CI 1.07-1.29, p=0.001) and reported more frequently jaw claudication (OR 3.52, 95% CI 1.02-13.16, p=0.051). PVL was present in 18 (42.9%) of the 42 patients with vasculitic ultrasound findings in all six temporal artery segments. The incidence of PVL over 15 years did not decline (Spearman-rank=0.3, p=0.68).

Conclusion: The prevalence of GCA-associated PVL remains high. Associated factors were advanced age, jaw claudication and ultrasound findings consistent with vasculitis in all six temporal artery segments. Despite preceding non-ocular GCA symptoms weeks before the onset of PVL, most patients were not seen by a rheumatologist before PVL occurred.

Key messages

What is already known on this topic:

- Permanent vision loss (PVL) is a feared complication of giant cell arteritis. Since the introduction of glucocorticoid treatment and fast-track clinics, the incidence of PVL has decreased but remains at 10-20%.

What this study adds:

- More than half of the patients experience GCA-related symptoms several weeks prior to the onset of PVL, but most do not seek medical advice until ocular symptoms occur.

This study might affect research, practice or policy:

- The still insufficient awareness of the symptoms, consequences, and treatment of GCA among care providers contributes to vision loss.
- Teaching of medical professionals and public education are needed to shorten diagnostic delays and thereby reduce the incidence of PVL in GCA patients

Introduction

The clinical presentation of giant cell arteritis (GCA) is heterogenous and includes constitutional and ischemic symptoms (1). The most severe complication remains permanent visual loss (PVL), mainly caused by anterior ischemic optic neuropathy (AION) involving the posterior ciliary arteries or central retinal artery occlusion (CRAO) (2). Less often, blindness results from posterior ischemic optic neuropathy (PION), or occipital lobe infarction (3). Before the advent of glucocorticoid therapy for GCA, PVL occurred in 40–48% (4–7) of cases and decreased to 10–20% during the last decades (8–14), due to an increased awareness of GCA-associated complications and the accepted practice among general practitioners (GPs) to immediately start systemic glucocorticoids in case of suspected GCA (15). If left untreated, the risk for bilateral AION is high (16). Transient visual symptoms, age, and lower blood levels of inflammatory markers are risk factors for impending vision loss (4,8,12,13,17–19). In contrast, polymyalgia and constitutional symptoms are associated with a reduced risk for PVL (4,11,13,18,20). In histopathological studies, PVL has been inconsistently associated with the presence of giant cells and higher intimal hyperplasia scores in temporal artery biopsy (21–24). Similarly, the detection of temporal arteritis by ultrasound has been associated with ocular ischemia in some studies (25,26).

Early diagnosis of GCA and immediate administration of glucocorticoids are essential to effectively prevent PVL, as most ocular ischemic events occur before treatment (8). However, once vision loss has occurred, it is usually permanent, and glucocorticoids are administered to preserve the remaining vision (4,27). The introduction of fast-track clinics, including ultrasound as a first-line diagnostic tool for early GCA diagnosis, intended to reduce the incidence of PVL even further compared with conventional clinical practice (28–30). In a recent study, a fast-track approach reduced PVL incidence by about 50%, but still, 12.7% experienced PVL (28). Obviously, patients can only be referred to fast-track clinics i) if they consult their GPs for

GCA-associated symptoms and ii) if their primary care physician suspects them of having GCA. The unspecific character of many GCA-associated symptoms may prevent patients from consulting with their GPs and result in misdiagnoses. A recent systematic review and meta-analysis reported a mean diagnostic delay between symptom onset and GCA diagnosis of nine weeks (31). This study aimed to investigate the incidence and risk factors of PVL among patients with GCA treated at our centre during the last 15 years and to identify obstacles in the patient's pathway that may cause a delay in treatment initiation.

Methods

Patients and setting

We performed a monocentric retrospective analysis of a cohort of patients referred to our clinic with suspected GCA. We routinely perform ultrasound examinations on all patients with suspicion of having GCA. Therefore, for case identification, we analysed all patients who had undergone ultrasound examination for diagnostic work-up of suspected GCA at the University Hospital Basel between December 2006 and May 2021. Of those, we included only patients with a final diagnosis of GCA and a follow-up period of at least six months after diagnosis. GCA was diagnosed if temporal artery biopsy was positive, if the 1990 criteria from the American College of Rheumatology (ACR) were fulfilled, or if at least 2/5 ACR criteria were fulfilled in combination with typical vasculitic findings in ultrasound, positron emission tomography with computed tomography (PET/CT), or magnetic resonance imaging (MRI) (32). This study was approved by the local Ethics committee (EKNZ, Project-ID 2021-00681).

Data collection

The following data were collected from the local Basel GCA cohort ('BARK') (33) and retrospective chart review: patients' demographics, clinical manifestations, the chronology of

symptoms, laboratory and imaging findings at the time of GCA diagnosis, results of ophthalmologic assessment, place and date of the first consultation, the reason for medical evaluation, date of diagnosis and date of glucocorticoid treatment initiation.

We defined visual impairment as vision loss, visual field loss, blurred vision, diplopia or amaurosis fugax associated with GCA. Transient visual impairment was defined as a temporary ocular symptom that resolved completely within six months of diagnosis. PVL was defined as complete vision loss or permanent visual field defect in at least one eye persisting six months after GCA diagnosis and occurring within six months after diagnosis. Consultation delay was defined as the time interval from GCA-attributable symptom onset to the first consultation with a health professional (31), and treatment delay as the time between the first consultation for GCA-related symptoms and initiation of glucocorticoid treatment.

Ultrasound

For ultrasound examinations, iU22 ultrasound devices with a linear 9-3 MHz and 17-5 MHz transducer or EPIQ 7 duplex devices with a linear 12-3 MHz and 18-5 MHz transducer (both from Philips, Best, The Netherlands) were used (34). An experienced angiologist (MA) reread and verified all ultrasound image classifications within the cohort. The following arterial segments were bilaterally categorised as 'normal', 'vasculitis', or 'arteriosclerosis': the common, internal, and external carotid arteries, subclavian and axillary arteries, and the superficial temporal arteries (trunk, parietal, and frontal branch). ‘Vasculitis’ in the temporal artery was detected using the compression sign (35). For larger vessels, ‘vasculitis’ was defined as previously described (33).

By analogy to the halo count (26), we calculated the number of affected (i.e. ‘vasculitis’) temporal artery segments (trunk, parietal, and frontal branches) on both sides, resulting in a maximum count of six. Patients with missing data in one or more temporal artery segments (e.g., due to temporal artery biopsy in this segment) were excluded from this analysis.

We separately calculated the number of vasculitis-affected segments for the carotid (common, internal, and external carotid arteries) and the subclavian/axillary arteries (Supplementary Table S1 and S2).

Statistical analysis

Continuous variables are presented as means with standard deviation (SD) or medians with interquartile ranges (IQR). Categorical variables are expressed as numbers with percentages. Baseline characteristics of patients who developed PVL within six months after diagnosis were compared to the rest of the cohort using the Student's t-test for data with parametric distributions. Data with non-parametric distributions were compared using the Mann-Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. Logistic regression analysis was applied to investigate the association between patient characteristics and PVL at six months after diagnosis, reported as odds ratios (ORs) with their 95% confidence intervals (CIs). Spearman's rank correlation was used to analyse the trend in the incidence of PVL (36). All statistical analyses were performed in RStudio version 2021.9.0.351 (2021-09-20).

Results

Study cohort

From December 2006 to May 2021, 740 patients with suspected GCA were screened by ultrasound at our center. GCA was diagnosed in 311 (42%) patients. Of those, 29 were excluded from the study because of missing follow-up (four patients died within one month after GCA diagnosis, and 25 patients were lost to follow-up) (Figure 1). In total, 282 patients (64% women) with a mean age of 72.9 ±8.3 years were included in the final analysis (Table 1).

Visual impairment and trend in the incidence of permanent vision loss

Transient and permanent visual impairment associated with GCA were recorded for 87 of 282 patients (30.9%) (Figure 2). In 38 (13.5%) patients with transient visual impairment, the most frequent symptoms were diplopia in 22 patients (57.9%) and blurred vision in 10 patients (26.3%). Abducens palsy was the most common diagnosis in 11/38 patients (28.9%). In 20 (52.6%) patients with transient visual impairment, fundus examination did not reveal any pathologic findings (Table 2). Two patients suffered from transient visual field loss, which resolved completely.

PVL occurred in 49/282 (17.4%) patients. Of these, 15/49 (30.6%) patients presented with complete blindness in at least one eye and 34/49 (69.4%) patients had permanent visual field loss. In 43/49 (87.8%) patients, PVL developed before therapy initiation, and the remaining six (12.2%) developed PVL with a median of 40.0 days (IQR 20.5-67.25) after treatment initiation. None of these six patients had visual symptoms at the initiation of treatment. Four of these patients were started on an initial dose of 40-60 mg of prednisone per day with a target dose of 15-20 mg/day within two to three months (Patients 44, 45, 48, 49, Supplementary Table S3). However, in two patients treated by their primary care physicians, prednisone was tapered too rapidly before vision loss occurred (Patients 46 and 47; Supplementary Table S3). The most common cause of PVL was AION in 36 of 49 patients (73.5%) followed by central CRAO in 8 of 49 patients (16.3%).

The proportion of patients who developed PVL has remained constant over the years (Spearman's rank correlation coefficient=0.3, p=0.68), although the number of cases evaluated for suspected GCA progressively increased, as did the number of patients diagnosed with GCA. From 2006 to 2013, 104 patients were diagnosed with GCA, of whom 17 (16.3%) experienced PVL. From 2014 to 2021, 178 patients were diagnosed with GCA, among whom PVL occurred in 32 patients (18.0%) (Supplementary Figure S1).

Findings associated with permanent vision loss

Patients with PVL were, on average, six years older (p<0.01), and more often reported jaw claudication (51.0 vs 35.2%, p=0.05) compared to those without PVL. Polymyalgia was less frequent in patients with PVL than those without PVL (22.4 vs 40.8%, p=0.03). Furthermore, patients with PVL were more likely to have comorbidities such as diabetes (32.7 vs 15.9%, p=0.006) and hypertension (63.3 vs 48.1%, p=0.05) (Table 1). Following multiple logistic regression, the variables age (OR 1.17, 95% CI 1.07-1.29, p = 0.001) and presence of jaw claudication (OR 3.52, 95% CI 1.02-13.16, p = 0.051) continued to be associated with PVL.

Colour duplex ultrasound findings

Of our cohort of 282 patients with GCA, a complete set of ultrasound images of all temporal artery segments was available for 248 patients (87.9%), including 42 patients with and 206 without PVL. In patients with PVL, a median of 4.5/6 temporal artery segments (IQR 2.0-6.0) showed vasculitic findings in ultrasound compared to a median of 1/6 temporal artery segments (IQR 0.0-4.0) in patients without PVL (p < 0.001). The incidence of PVL was highest when all six temporal artery segments were affected; of 42 patients with vasculitis in all segments, 18 (42.9%) presented with PVL. Of note, 8/42 patients (19.0%) without ultrasound findings in the temporal artery segments presented with PVL (Figure 3).

We also investigated the association between ocular ischemia and vasculitis-affected segment counts for the carotid/subclavian/axillary arteries. The number of extratemporal affected segments did not differ between patients with PVL and patients without PVL (Supplementary Tables S1-S2).

Chronology of GCA manifestations, consultation and treatment delay in patients with PVL

In 19 of the 43 (44.2%) patients presenting with PVL before glucocorticoid initiation, vision loss was the first symptom of GCA (Supplementary Table S4, cases 1-19). In the remaining 24/43 patients (55.8%), ischemic or constitutional symptoms had preceded the onset of PVL (Supplementary Table S4, cases 20-43).

Consultation delay was shorter in patients who reported vision loss as their first symptom (median 2.0 days after symptom onset, IQR 1.0-3.0 days) than patients with preceding non-ocular GCA-related symptoms (median 21 days after symptom onset, IQR 14.75-31.0 days). Of the latter, the majority consulted a physician only once they suffered visual impairment (Supplementary Table S4, case 20-38). Five subjects had consulted a physician before PVL, but the diagnosis of GCA was not considered at that time and no glucocorticoid treatment was initiated until PVL developed later on (Supplementary Table S4, case 39-43). Detailed case descriptions of these five patients are found in the supplementary material. The remaining patients who did not develop PVL (n=233) consulted a physician a median of 12 days (IQR 6.0-25.0) after symptom onset, which is significantly faster compared to the 24 patients with PVL and preceding GCA-related symptoms ($p = 0.005$).

Treatment for patients reporting visual impairment started on the same day as the first medical contact (median 0.0 days, IQR 0.0-3.5). In patients without visual impairment, treatment was initiated a median of two days after first medical contact (IQR 0.0-8.0).

Discussion

More than 17% of all 282 patients with GCA experienced either partial (12.1%) or complete (5.3%) PVL within six months of diagnosis, which is within the range of previously published studies (8–14). The incidence of PVL over the studied period spanning 16 years remained

stable. Although symptoms of GCA were present for weeks in a large proportion of patients, most patients sought medical care only after vision loss had occurred. Treatment was started immediately once the diagnosis of GCA was made. Six patients developed PVL despite established glucocorticoid therapy. This is in line with a recent study reporting the incidence of new PVL after initiation of glucocorticoid therapy to be 2.2% (37). Consistent with previous studies, AION was the most common cause of PVL (3,8).

After multivariable analysis, we could confirm older age (8,38) and jaw claudication as risk factors for PVL (9,38,39). Conflicting results have been described concerning the association of inflammatory markers with the occurrence of PVL. We found no significant difference in CRP and ESR values between patients with and without PVL, which corroborates data from previous studies (13,38,39). Others suggested that a strong acute-phase response identifies patients at low risk of PVL (17), and that a normal ESR is a risk factor for PVL (8).

The vasculitis-affected segment count of the temporal arteries by ultrasound was significantly higher in patients with PVL than in those without PVL. Most strikingly, when all six temporal artery segments were affected by vasculitis, the prevalence of PVL was 42.9%. However, almost one out of five patients with PVL had a negative ultrasound of the temporal arteries. Thus, treatment should not be delayed in ultrasound-negative patients.

Van der Geest et al. also showed that the extent of ultrasound-defined vascular inflammation of the temporal and axillary arteries is linked to ocular ischemia in patients with GCA (26). One previous study by Schmidt et al. did not find any association between ultrasound findings and the occurrence of ocular ischemia (25). However, the definition of ocular ischemia in the study of Schmidt et al. was broader and included transient symptoms such as diplopia and amaurosis fugax which might explain some discrepancies. Patients with 6/6 temporal artery segments showing vasculitis in ultrasound may be at risk for imminent vision loss and immediate, intense treatment is suggested.

The PVL incidence of 17.4% in our cohort was similar to that reported by Gonzalez-Gay et al. (14.9%) (11), Cid et al. (14.0%) (17), or Salvarani et al. (19.1%) (8). In contrast to previously described fast-track clinic approaches, we could not confirm a reduction in the incidence of PVL over time (28,29). However, the recommendation to immediately initiate glucocorticoid therapy upon suspicion of GCA is broadly followed by primary care physicians in Switzerland. Therefore, the formal implementation of a fast-track clinic in our hospital in 2014 might not have significantly impacted the speed of the appropriate management of patients with suspected GCA. More difficult healthcare access in other countries, regional differences, smaller sample sizes (30), potential selection biases due to an increased rate of referrals with less severe manifestations and high numbers of patients with large-vessel GCA (28–30), as well as different definitions of PVL (we included all patients having experienced PVL within the first six months after diagnosis) may explain differences in the impact of fast-track clinics between the cohorts.

In contrast to the effects of fast-track clinics, the management and disease course of patients with GCA before diagnosis have not been studied to date. The time interval from the first symptom to treatment initiation is critical for preventing vision loss. We, therefore, considered both the time from symptom onset to the initial consultation, and the time from initial consultation to therapy initiation for their potential contribution to the development of PVL. Indeed, the time between GCA symptom onset and the first consultation contributed most to the delay in therapy initiation and was the longest in patients with PVL with preceding symptoms.

Five of 43 patients who experienced vision loss before the initiation of treatment had consulted a physician for GCA-related symptoms prior to vision loss but were misdiagnosed. In two of six patients who experienced vision loss after the initiation of glucocorticoid treatment, a GCA diagnosis was made by their primary care provider, but glucocorticoid tapering was inadequate.

Patients without PVL sought significantly earlier medical care. This potentially prevented PVL in some of them. We can only suspect that the nonspecific nature of some GCA symptoms precluded some patients from seeking medical attention. Increasing age was associated with PVL in our cohort. Therefore, the older age, associated limited mobility, and a potential reluctance to seek medical help may have contributed to the delay between symptom onset and consultation among these patients. If the diagnosis of GCA was eventually made, therapy was started rapidly, irrespective of the physician's specialization. This reflects common knowledge amongst all physicians to immediately start glucocorticoid treatment upon suspicion of GCA and then refer patients for further diagnostics (4,40).

PVL in most cases occurred before presentation to fast-track clinics. Therefore, future strategies for preventing GCA-related damage should focus on the patients' disease course before the referral to fast-track clinics by raising public awareness for GCA. Furthermore, medical education of students and postgraduate teaching of the different presentations and of the adequate treatment of GCA is necessary to prevent misdiagnoses and inappropriate management of patients with GCA.

The major limitation of our study is its retrospective design. Although we found that consultation delay is the longest in patients with PVL with preceding symptoms, specific reasons for the consultation delay remain unknown.

Conclusion

PVL was found in 17% of newly diagnosed GCA patients despite recent advances in GCA management and the implementation of fast-track clinics. Older age, jaw claudication and a high number of vasculitis-affected temporal artery segments are associated with PVL. Whereas immediate treatment in case of suspicion of GCA is implemented in general practice, there was still a substantial delay from symptom onset to diagnosis, which was the longest for patients presenting with PVL. Consequently, public and physician awareness of the various GCA

symptoms should be raised. The patient's journey until diagnosis of GCA needs to be further and prospectively studied.

Conflict of interests

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Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

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Table and figure legends

Table 1: Patient characteristics at the time of diagnosis

Table 2: Ocular symptoms and diagnoses of patients with visual involvement

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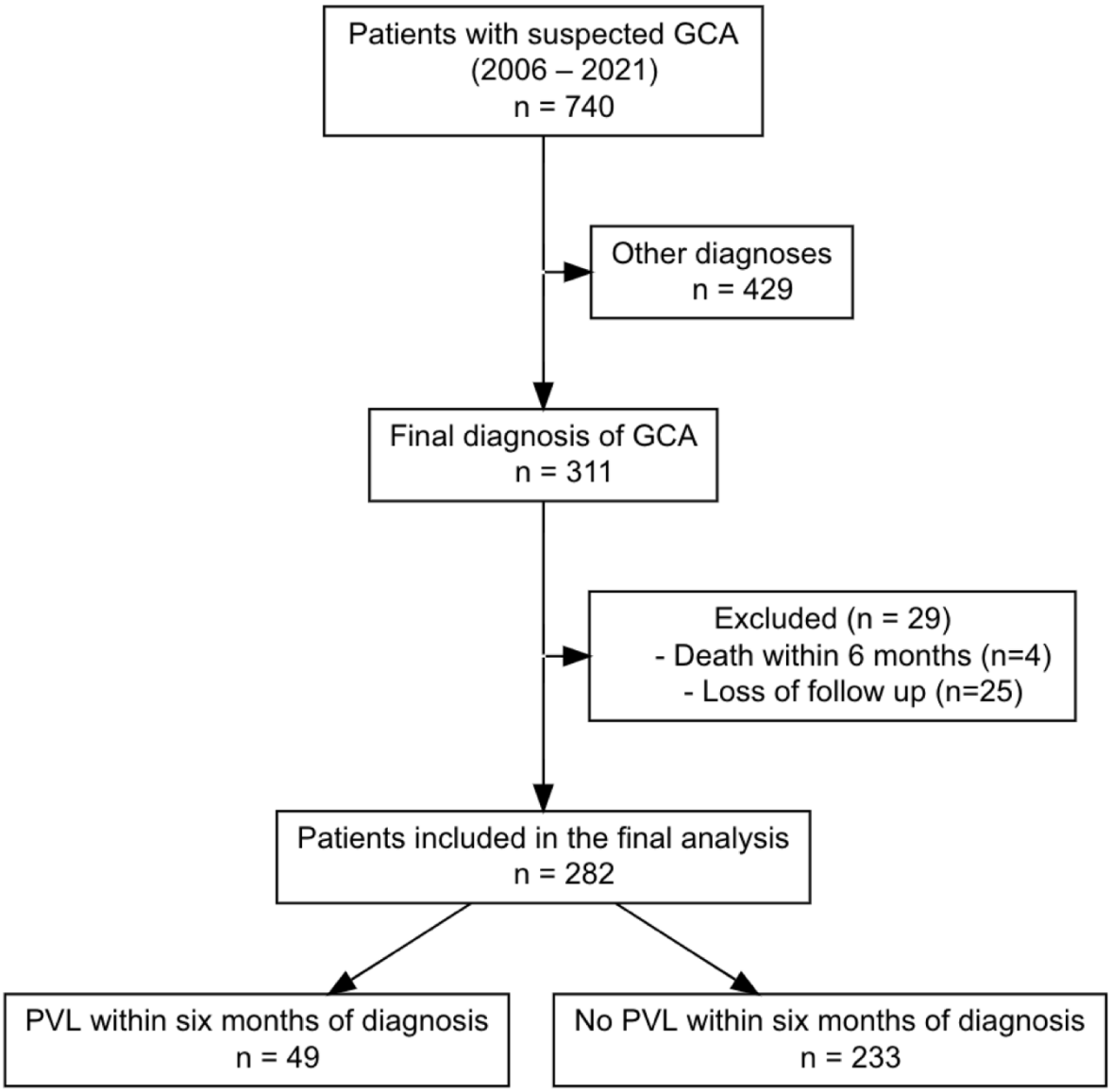
Figure 2: Patients with giant cell arteritis (GCA) and visual impairment (permanent and transient). Half of all patients had GCA-related symptoms before onset of visual impairment.

Figure 3: Number of segments with colour duplex ultrasound defined vasculitis in the temporal arteries (trunk, parietal and frontal branches on both sides) in patients with permanent vision loss (PVL) compared to patients without PVL.

Table 1: Patient characteristics at the time of diagnosis				
Characteristics	**All**	**PVL**	**No PVL**	**p-value**
Number of patients, n (%)	282	49 (17.4)	233 (82.6)	-
Age, mean (±SD)	72.9 (±8.3)	77.8 (±7.5)	71.8 (±8.2)	<0.01
Female, n (%)	180 (63.8)	27 (55.1)	153 (65.7)	0.16
BMI, mean (±SD)	25.1 (±5.0)	24.3 (±4.7)	25.3 (±5.1)	0.64
History of PMR, n (%)	44 (15.6)	7 (14.3)	37 (15.9)	0.73
Hypertension, n (%)	143 (50.7)	31 (63.3)	112 (48.1)	0.05
Diabetes mellitus, n (%)	53 (18.8)	16 (32.7)	37 (15.9)	0.006
Dyslipidemia, n (%)	71 (25.2)	16 (32.7)	55 (23.6)	0.09
Smoking, n (%)	94 (33.3)	15 (30.6)	79 (33.9)	0.72
Coronary artery disease, n (%)	40 (14.2)	7 (14.3)	33 (14.2)	0.99
Cerebrovascular disease, n (%)	35 (12.4)	5 (10.2)	30 (12.9)	0.59
Peripheral artery disease, n (%)	25 (8.9)	7 (14.3)	18 (7.7)	0.17
ESR, median (IQR)	70 (40-89)	70 (54-80)	72 (40.0-90.0)	0.75
CRP, median (IQR)	56.9 (27.20-108.8)	44.4 (27.7-90.6)	60.9 (27.3-110.5)	0.26
Leukocytes, median (IQR)	9.9 (8.1-11.7)	10.13 (8.4-11.7)	9.77 (7.9-11.8)	0.34
Thrombocytes, median (IQR)	381 (305.0-485.2)	384 (280.0-468.0)	380 (315.0-493.5)	0.49
Hemoglobin, mean (±SD)	122.0 (±15.6)	121.2 (±17.7)	122.1 (±15.2)	0.73
Fever, n (%)	38 (13.5)	3 (6.1)	35 (15.0)	0.09
Headache, n (%)	169 (59.9)	27 (55.1)	142 (60.9)	0.54
Jaw claudication, n (%)	107 (37.9)	25 (51.0)	82 (35.2)	0.05
Scalp tenderness, n (%)	97 (34.4)	15 (30.6)	82 (35.2)	0.75
Weight loss, n (%)	105 (37.2)	18 (36.7)	87 (37.3)	0.82
Polymyalgic symptoms, n (%)	107 (37.9)	11 (22.4)	95 (40.8)	0.03
Tenderness of the TA, n (%)	83 (29.4)	18 (36.7)	65 (27.9)	0.16
Abbreviations: CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; IQR=interquartile range; n=number; PMR=Polymyalgia rheumatica; PVL=permanent vision loss; SD=standard deviation; TA=temporal artery.				

Table 2: Ocular symptoms and diagnoses of patients with visual impairment				
Symptoms*	**All (n=87)**	**PVL (n=49)**	**TVI (n=38)**	**p-value**
Vision loss, n (%)	24 (27.6)	24 (49.0)	0 (0.0)	<0.001
Diplopia, n (%)	23 (26.4)	1 (2.0)	22 (57.9)	<0.001
Visual field loss, n (%)	22 (25.3)	20 (40.8)	2 (5.3)	<0.001
Blurred vision, n (%)	19 (21.8)	9 (18.4)	10 (26.3)	0.37
Amaurosis fugax, n (%)	9 (10.3)	2 (4.1)	7 (18.4)	0.04
Diagnoses	**All (n=87)**	**PVL (n=49)**	**TVI (n=38)**	**p-value**
AION, n (%)	37 (42.5)	36 (73.5)	1 (2.6)	<0.001
Abducens palsy, n (%)	11 (12.6)	0 (0.0)	11 (28.9)	<0.001
CRAO, n (%)	8 (9.2)	8 (16.3)	0 (0.0)	0.009
CVI, n (%)	5 (5.7)	1 (2.0)	4 (10.5)	0.16
INOP, n (%)	1 (1.1)	0 (0.0)	1 (2.6)	0.44
Normal findings in the examination, n (%)	20 (23.0)	0 (0.0)	20 (52.6)	<0.001
PION, n (%)	1 (1.1)	1 (2.0)	0 (0.0)	1
No examination, n (%)	1 (1.1)	1 (2.0)	0 (0.0)	1
AION + CRAO, n (%)	1 (1.1)	1 (2.0)	0 (0.0)	1
AION + CVI, n (%)	1 (1.1)	0 (0.0)	1 (2.6)	0.44
AION + abducens palsy, n (%)	1 (1.1)	1 (2.0)	0 (0.0)	1
*Some patients had more than one symptom.				
Abbreviations: AION=anterior ischemic optic neuropathy; CRAO= central retinal artery occlusion; CVI=cerebrovascular insult; INOP= internuclear ophthalmoplegia; n=number; PION=posterior ischemic optic neuropathy; TVI=transient visual impairment.				



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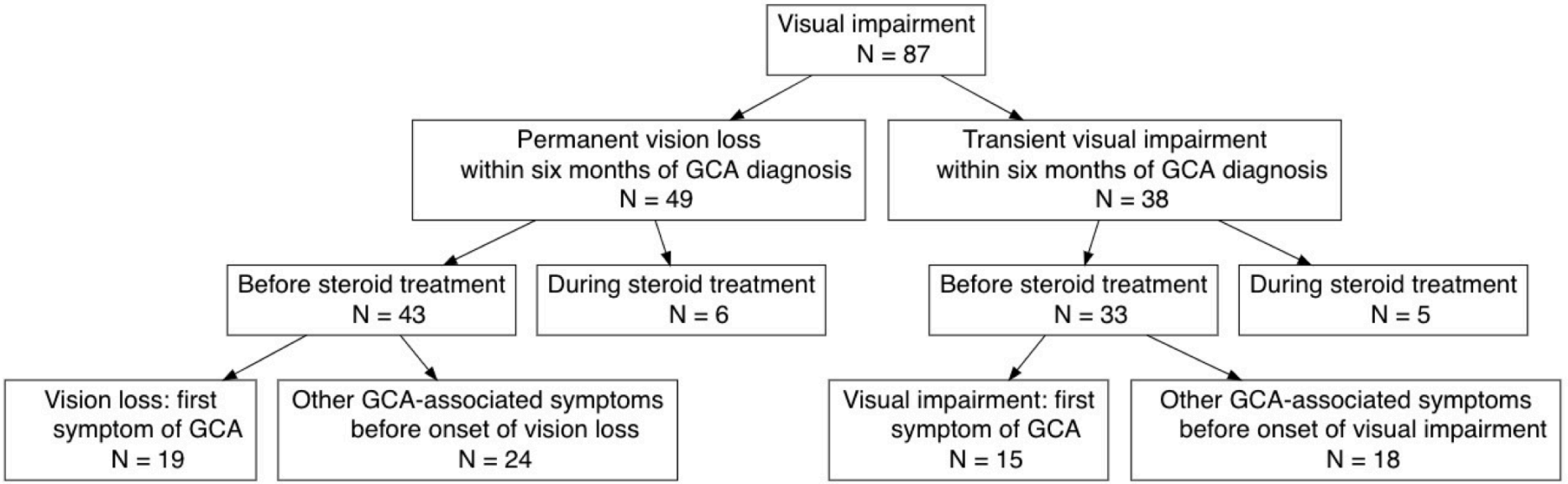

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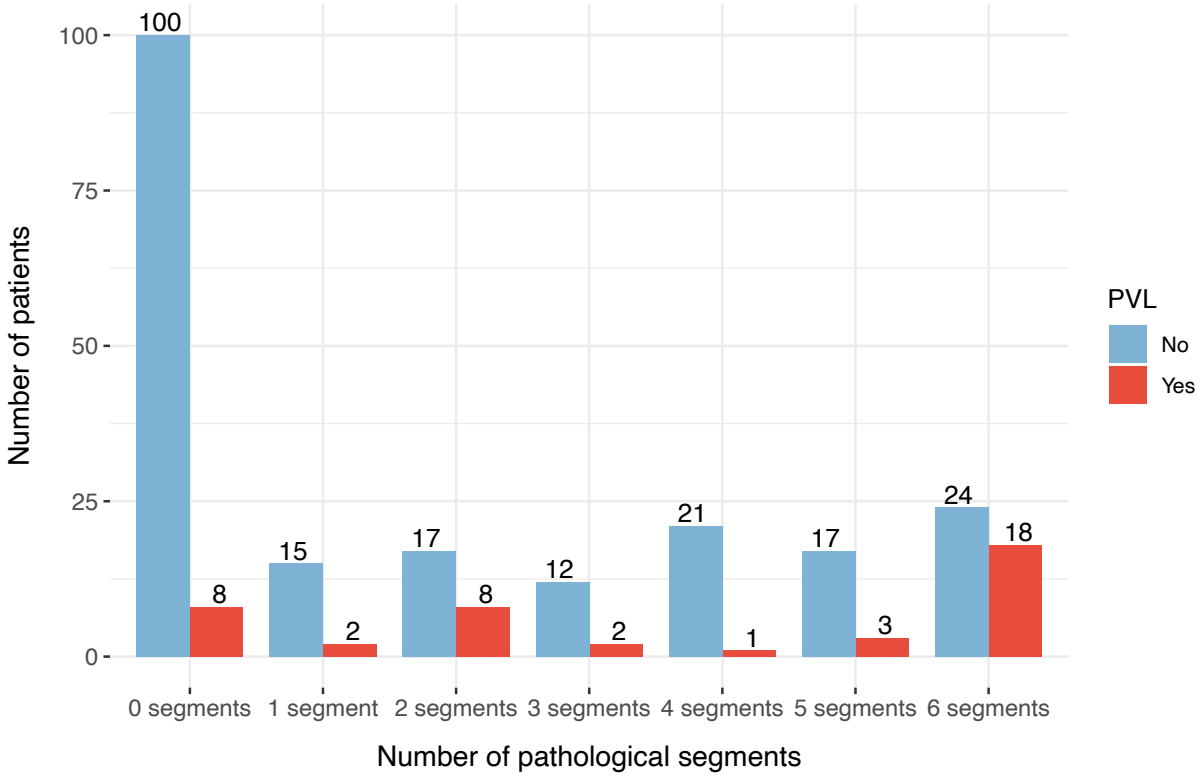


Figure 3: Number of segments with colour duplex ultrasound defined vasculitis in the temporal arteries (trunk, parietal and frontal branches on both sides) in patients with permanent vision loss (PVL) compared to patients without PVL.

Supplementary Material

Vasculitis counts

The number of segments categorized as vasculitis for the carotid arteries are shown. Additionally, we summarized the subclavian and axillary arteries as one segment, resulting in a total vasculitis score of two points per patient.

We only included patients with complete ultrasonographic examinations of the respective segments.

Supplementary Table S1: Number of segments categorized as vasculitis of the common, internal, and external carotid arteries on both sides (total of 6 points)

	Without PVL	**With PVL**	**p-value**
Number of patients	223	45	-
Median (IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.9701
Abbreviations: IQR=interquartile range; PVL=permanent vision loss			

Supplementary Table S2: Number of segments categorized as vasculitis of the subclavian/axillary segment on both sides (total of 2 points)

	Without PVL	**With PVL**	**p-value**
Number of patients	227	44	-
Median (IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.7951
Abbreviations: IQR=interquartile range; PVL=permanent vision loss			

Supplementary Table S3: Characteristics of patients with vision loss during steroid treatment. Eleven of 87 patients with visual impairment (12.6%) had not shown any ocular manifestations at first consultation but developed visual impairment after treatment had been commenced, of whom six patients developed PVL.

Case	Sex	Partial or complete vision loss in at least one eye	First symptoms	Reason for seeking medical advice	Consultation delay (days)	Treatment delay (days)	Starting GC dose (mg)	Timepoint of permanent vision loss in relation to first consultation	GC dose at the time of vision loss (mg)	Time from treatment initiation to vision loss (days)	Ophthalmologic diagnosis
Patient 44	f	partial	Headache and jaw claudication	Headache and jaw claudication	28	2	60	After first consultation	60	3	CVI
Patient 45	m	partial	Headache	Headache, weight loss	0	33	60	After first consultation	10	141	AION right eye
Patient 46	f	complete	Jaw claudication, headache, weight loss	Jaw claudication, headache	2	2	40	After first consultation	5	15	CRAO right eye
Patient 47	m	partial	Neck pain and headache	Neck pain, headache, painful temporal artery and jaw claudication	7	0	50	After first consultation	15	37	CRAO left eye
Patient 48	m	partial	Fever, deterioration of the patient's general condition	Fever, deterioration of the patient's general condition	97	30	60	After first consultation	15	75	CRAO right eye
Patient 49	f	partial	Jaw claudication	Jaw claudication	2	0	40	After first consultation	30	44	AION left eye, abducens palsy right eye

Abbreviations: AION=anterior ischemic optic neuropathy; CRAO=central retinal artery occlusion; f=female; CVI=cerebrovascular insult; GC=glucocorticoid; GP=general practitioner; m=male.

Supplementary Table S4: Characteristics of patients with vision loss before steroid treatment initiation.

Case	Sex	Partial or complete vision loss in at least one eye	First GCA-associated symptoms	Reason for seeking medical advice	Consultation delay (days)	Treatment delay (days)	Place of first consultation	Timepoint of permanent vision loss	Ophthalmologic diagnosis
Case 1	f	partial	Vision loss right eye	Vision loss right eye	1	0	Emergency department	Before first consultation	AION right eye
Case 2	f	complete	Vision loss left eye	Vision loss left eye	1	0	Eye clinic	Before first consultation	AION left eye
Case 3	f	complete	Vision loss right eye	Vision loss right eye	3	0	Eye clinic	Before first consultation	CRAO right eye
Case 4	m	partial	Visual field loss left eye	Visual field loss left eye	1	0	Eye clinic	Before first consultation	AION left eye
Case 5	m	partial	Vision loss left eye	Vision loss left eye	2	0	GP	Before first consultation	AION left eye
Case 6	m	partial	Vision loss left eye	Vision loss left eye	2	0	GP	Before first consultation	AION left eye
Case 7	f	partial	Visual field loss left eye	Visual field loss left	1	1	Other	Before first consultation	AION left eye
Case 8	f	partial	Vision loss and blurred vision on both sides	Vision loss and blurred vision on both sides	2	2	Private ophthalmology practice	Before first consultation	AION on both sides
Case 9	m	partial	Vision loss left eye	Vision loss left eye	5	1	Private ophthalmology practice	Before first consultation	CRAO left eye
Case 10	m	partial	Vision loss left eye	Vision loss left eye	3	11	Private ophthalmology practice	Before first consultation	AION left eye
Case 11	m	partial	Visual field loss left eye	Visual field loss left eye	3	0	Private ophthalmology practice	Before first consultation	AION left eye
Case 12	m	partial	Visual field loss on both sides	Visual field loss on both sides	15	0	Private ophthalmology practice	Before first consultation	PION on both sides
Case 13	f	partial	Visual field loss on both sides, painful temporal artery, jaw claudication	Visual field loss on both sides, painful temporal artery, jaw claudication	1	0	Eye clinic	Before first consultation	AION on both sides
Case 14	m	partial	Visual field loss, headache, scalp tenderness, jaw claudication, weight loss and night sweats	Visual field loss, headache, scalp tenderness, jaw claudication, weight loss and night sweats	NA	NA	Eye clinic	Before first consultation	AION on both sides
Case 15	f	complete	Vision loss left, headache, jaw claudication	Vision loss left, headache, jaw claudication	NA	NA	GP	Before first consultation	AION left eye
Case 16	f	complete	Vision loss right eye, blurred vision left eye, jaw pain	Vision loss right eye, blurred vision left eye, jaw pain	3	0	GP	Before first consultation	AION on both sides
Case 17	f	complete	Vision loss left eye, headache	Vision loss left eye, headache	2	0	Private ophthalmology practice	Before first consultation	NA
Case 18	m	partial	Vision loss right eye, followed by jaw claudication	Vision loss right eye and jaw claudication	14	0	Private ophthalmology practice	Before first consultation	AION right eye
Case 19	f	partial	Visual field loss right eye, headache	Visual field loss right eye and headache	3	0	Private ophthalmology practice	Before first consultation	AION right eye
Case 20	f	partial	Headache	Vision loss right eye	31	0	Emergency department	Before first consultation	AION right eye
Case 21	f	complete	Neck pain and headache	Vision loss left eye	31	0	Emergency department	Before first consultation	CRAO left eye
Case 22	f	complete	Headache	Vision loss right eye	19	1	Eye clinic	Before first consultation	AION right eye
Case 23	m	partial	Headache	Vision loss left eye	6	0	Eye clinic	Before first consultation	AION left eye
Case 24	f	partial	Headache	Visual field loss right eye	22	0	Eye clinic	Before first consultation	AION right eye

Case	Sex	Partial or complete vision loss in at least one eye	First GCA-associated symptoms	Reason for seeking medical advice	Consultation delay (days)	Treatment delay (days)	Place of first consultation	Timepoint of permanent vision loss	Ophthalmologic diagnosis
Case 25	m	complete	Headache, jaw claudication and scalp tenderness	Vision loss right eye, visual field loss left eye	9	0	Eye clinic	Before first consultation	AION on both sides
Case 26	m	partial	Jaw claudication	Visual field loss left eye	13	1	Eye clinic	Before first consultation	AION left eye
Case 27	m	complete	Jaw claudication followed by hip pain and headache	Vision loss and blurred vision on both sides	23	0	Eye clinic	Before first consultation	AION on both sides
Case 28	f	partial	Neck pain and headache	Blurred vision left eye	59	1	Eye clinic	Before first consultation	AION left eye
Case 29	M	partial	Neck pain followed by jaw claudication and headache	Visual field loss left eye	15	0	Eye clinic	Before first consultation	AION left eye
Case 30	F	partial	Night sweats, weight loss	Blurred vision right eye	14	0	Eye clinic	Before first consultation	AION right eye
Case 31	M	partial	Shoulder and neck pain followed by jaw claudication and scalp tenderness	Visual field loss on both sides	92	0	Eye clinic	Before first consultation	AION on both sides
Case 32	M	partial	Jaw claudication, deterioration of the patient's general condition, weight loss	Visual field loss	30	1	GP	Before first consultation	AION right eye
Case 33	F	complete	Neck pain, jaw claudication	Vision loss left eye	25	0	GP	Before first consultation	AION left eye
Case 34	F	complete	Headache, weight loss	Vision loss on both sides	416	0	Private ophthalmology practice	Before first consultation	CRAO left eye, AION right eye
Case 35	F	partial	Neck pain and headache	Visual field loss left eye	21	1	Private ophthalmology practice	Before first consultation	CRAO left eye
Case 36	F	partial	Night sweats	Blurred vision left eye	196	7	Private ophthalmology practice	Before first consultation	AION left eye
Case 37	F	complete	Scalp tenderness, jaw claudication, pain in the temporal artery	Vision loss left eye	19	0	Private ophthalmology practice	Before first consultation	AION right eye
Case 38	f	partial	Shoulder and neck pain	Blurred vision left eye	21	3	Private ophthalmology practice	Before first consultation	AION left eye
Case 39	m	partial	Amaurosis fugax right eye	Amaurosis fugax right eye	0	49	Different hospital	After first consultation	AION right eye
Case 40	f	partial	Headache, jaw claudication	Headache, jaw claudication	18	10	Different hospital	After first consultation	AION right eye
Case 41	m	complete	Headache	Headache, deterioration of the patient's general condition	21	11	GP	After first consultation	AION left eye
Case 42	f	complete	Headache and jaw claudication	Headache, jaw claudication, fever	10	3	GP	After first consultation	AION right eye
Case 43	m	partial	Headache, fever, weight loss	Headache, fever, weight loss	35	11	GP	After first consultation	CRAO right eye

Consultation delay=time from GCA symptom onset to first consultation; treatment delay=time from first consultation to treatment initiation.
Abbreviations: AION=anterior ischemic optic neuropathy; CRAO=central retinal artery occlusion; f=female; GP=general practitioner; NA=not available; m=male; PION=posterior ischemic optic neuropathy.

Supplementary case descriptions

Five of 43 patients who suffered from vision loss before steroid initiation were shown to have sought medical advice in advance, when visual symptoms were not yet present. These five cases illustrate the difficulty in diagnosing giant cell arteritis (GCA), which was not recognized in these cases until after the onset of irreversible visual disturbances.

Case 39 (Table 3)

A patient with a previous history of polymyalgia rheumatica had suffered from a single episode of amaurosis fugax in the right eye, whereupon the patient presented at the same day as symptom onset. Extensive examinations including cerebrovascular imaging were performed and excluded intracranial hemorrhage, stroke, or tumor. An ultrasonography examination showed no evidence of GCA. Due to inconclusive results, no steroid treatment was initiated. Weeks later, the patient self-referred and reported a two-week history of progressively decreasing vision in the right eye and concomitant weight loss. At presentation, the patient suffered from visual field loss and fundoscopy revealed optic disc oedema. Ultrasonography showed new vasculitic changes in the temporal artery on both sides.

Case 40 (Table 3)

A patient presented with severe new-onset headache and jaw pain. Cerebral imaging was not conducted; however, it was not possible to determine from the medical records which examinations were performed. Steroid treatment, however, was not initiated. Nine days later, the patient suffered from sudden vision loss and presented directly at the emergency department of our clinic. Bedside ultrasonography showed positive compression signs on both sides of the frontal temporal artery and the ophthalmologic examination revealed optic disc edema and temporal visual field loss. High-dose glucocorticoid treatment was promptly initiated, however, visual field loss remained irreversible.

Case 41 (Table 3)

A patient was referred to a hospital by his GP due to deterioration of the patient's health and new-onset headache. Laboratory results revealed an elevated C-reactive protein and leucocytosis. A thoracic CT scan revealed pneumonia, which was treated with antibiotics. In the further course, the patient developed sudden visual disturbances in his left eye up to complete vision loss. Steroid treatment was started, and the patient was referred to our clinic for further diagnostics.

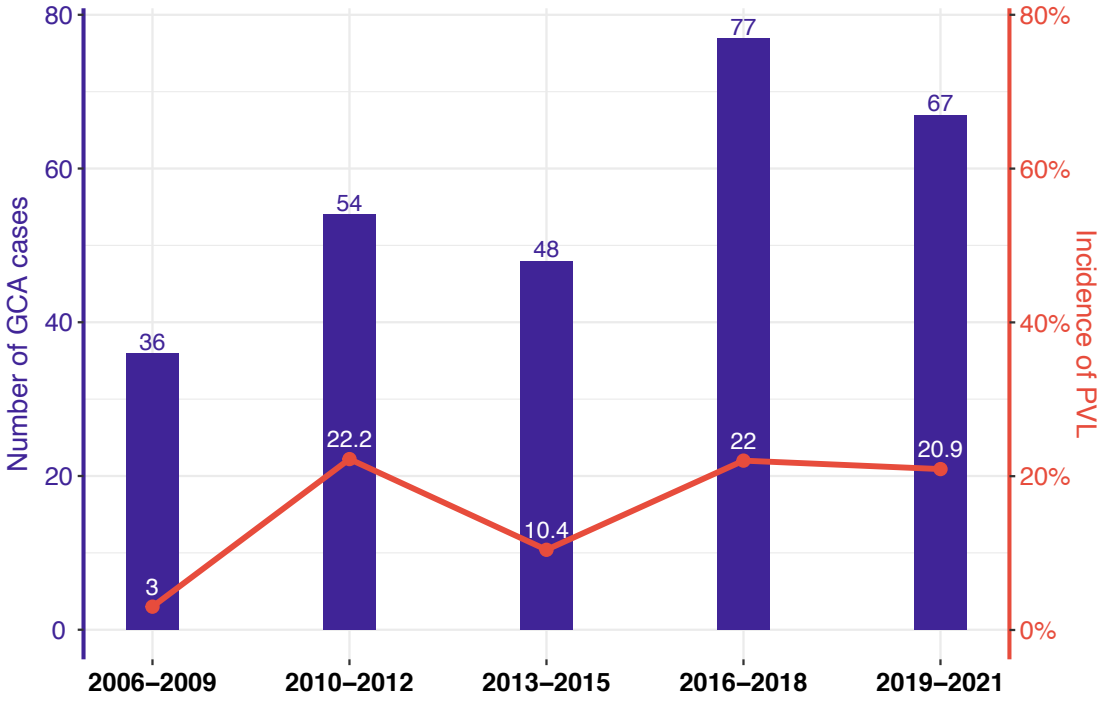
Case 42 (Table 3)

A patient first suffered from jaw claudication and intermittent headache. During that time, the patient consulted a dentist due to persistent jaw pain. Since the dental examination remained inconclusive, no therapy was initiated. However, on the same day, the patient consulted her general practitioner (GP) due to headache and new onset fever. Additionally, the patient reported abdominal pain which prompted her GP to refer the patient to the emergency department. Due to the unspecific nature of the symptoms with predominant constipation, an abdominal infection was excluded and empiric antibiotic therapy was initiated on admission. In the further course, the patient developed painful temporal arteries and acute amaurosis on her right eye. An emergency ophthalmological, neurological and rheumatological evaluation was performed and due to suspected anterior ischemic optic neuropathy (AION) and GCA, high-dose intravenous steroid treatment was started immediately. Unfortunately, complete blindness persisted in the right eye.

Case 43 (Table 3)

A patient consulted his GP complaining of headache, fatigue, loss of appetite, night sweats as well as weight loss for over a period of one month. His GP initiated an antibiotic therapy which did not improve the patient's symptoms and a thoracic CT scan remained inconclusive. After a couple of days, the patient experienced a sudden episode of transient blurred vision in both eyes

and subsequent complete blindness in his right eye. He consulted a private ophthalmologist, who referred him immediately with suspicion of GCA.



Supplementary Figure S1: Number of patients diagnosed with giant cell arteritis at the University Hospital Basel from December 2006 to May 2021. The line indicates the trend in incidence (%) of permanent vision loss (PVL) over the last 15 years.

4.3 Manuscript III: Magnetic resonance imaging findings corresponding to vasculitis as defined by [^{18}F]FDG positron emission tomography or ultrasound

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Key words: Giant cell arteritis, imaging, vasculitis, magnetic resonance imaging, ultrasonography

Abstract

Objectives: To investigate magnetic resonance imaging (MRI) parameters which correspond to vasculitis on [^{18}F]FDG positron emission tomography/computed tomography (PET/CT) or ultrasound in patients with large vessel giant cell arteritis (LV-GCA).

Methods: Cross-sectional analysis of patients diagnosed with LV-GCA between 01/2019–03/2023. Patients were selected if MRI, PET/CT, and vascular ultrasound were performed at LV-GCA diagnosis. Imaging findings in vessel segments (axillary segment per side, thoracic aorta) assessed by at least two methods were compared. Vessel wall thickening, oedema and contrast-agent enhancement each were assessed on MRI.

Results: Twelve patients with newly diagnosed LV-GCA were included (seven females, 58%; median age 72.1, IQR 65.5–74.2 years). MRI showed mural thickening in 9/24 axillary artery segments. All but one segment showed concomitant oedema, and additional contrast enhancement was found in 3/9 segments. Eight of these 9 segments corresponded to vasculitic findings in the respective segments on PET/CT and 2/9 to vasculitis in the respective ultrasound images. If MRI was performed more than 6 days after starting prednisone treatment, thickening and oedema was seen in only 1/24 segments, which was also pathologic on ultrasound but not on PET/CT.

Four patients had mural thickening, oedema and contrast enhancement in the aorta of which three patients had also vasculitic findings on PET/CT. Isolated mural thickening in one patient corresponded to a negative PET/CT.

Conclusion: On MRI, mural thickening due to oedema corresponded with vasculitic PET/CT findings but not with vasculitic ultrasound findings. Duration of steroid treatment may reduce sensitivity of MRI.

Key messages

- Vessel wall oedema in the DWI MRI sequence corresponds to active vasculitis on PET/CT.
- MRI findings agree poorly with ultrasound defined vasculitis.
- Duration of steroid treatment impacts on sensitivity of MRI.

Introduction

Giant cell arteritis (GCA) is the most common primary vasculitis of the elderly. Patients with large vessel GCA (LV-GCA) may present with an isolated systemic inflammatory syndrome and imaging is necessary to establish the diagnosis (1). Different imaging techniques measure different characteristics of the vessel wall in patients with LV-GCA. Magnetic resonance imaging (MRI) assesses vessel wall morphology, oedema and capillary leaking by contrast enhancement (2–4). [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) measures metabolic activity via glucose uptake (5,6) and ultrasound measures wall thickening based on echogenicity by emitting sound waves (7). For PET/CT and ultrasound, qualitative and quantitative parameters that define vasculitis have been proposed and are widely used (8). In contrast to its use for diagnosing cranial GCA (2,3), magnetic resonance imaging (MRI) is poorly standardised for the diagnostics of LV-GCA and only few studies exist on the diagnosis of extracranial LV-GCA by MRI (9–15). Furthermore, studies comparing MRI with other imaging modalities are sparse and have limitations due to different approaches for MRI interpretation and heterogenous patient populations including patients with Takayasu arteritis (12,13,15).

The aim of this study was to identify which MRI parameters correspond to PET/CT or ultrasound defined vasculitic segments in patients with LV-GCA.

Methods

Patients and setting

This is a cross-sectional analysis of a prospective MRI study (ClinicalTrials.gov identifier: NCT04204876) of patients diagnosed with LV-GCA between January 2019 and March 2023 at the University Hospital Basel, Switzerland. Patients with suspected LV-GCA are routinely screened by ultrasound of the supra-aortic vessels and PET/CT. Eight patients with newly

diagnosed LV-GCA on PET/CT underwent a prospective thoracic study MRI in the frame of our local Ethics committee approved MRI study (EKNZ Project-ID 2019-02161). In addition, we included 4 patients from our local GCA cohort that underwent all three imaging modalities but were not prospectively included (Basler Riesenzellarteriitis Kohorte [BARK EKNZ, #239/09]). All three imaging modalities were performed at diagnosis. The final diagnosis of LV-GCA was made if (i) temporal artery biopsy was positive or (ii) at least 2 of 5 1990 American College of Rheumatology criteria were fulfilled in combination with PET/CT findings typical for large vessel vasculitis (LVV) (16). All patients provided written informed consent. Patient characteristics are summarized in Supplementary Table S1.

MRI acquisition and assessment

MRI examinations were performed on a 1.5 T clinical MRI system (Magnetom Avanto fit, Siemens Healthineers, Erlangen, Germany) using the sequence protocol listed in Supplementary Table S2. For contrast enhanced imaging, a Gadolinium-based contrast agent (Gadobutrol (Gadovist ®), Bayer AG, Leverkusen, Germany) was applied in the standard dose of 0,1 mmol Gd/kg body weight. Pathological MRI findings (i.e., mural thickening, late mural enhancement and mural oedema) were assessed by a board-certified radiologist (G.S., 8 years of experience) subspecialized in cardiovascular imaging, blinded for the clinical data, PET/CT scan and ultrasound results. Mural thickening was scored as: 0 (no mural thickening), 1 (mild mural thickening, 2-3 mm for aorta, 1-2 mm for the subclavian/axillary artery), or 2 (strong thickening, >3 mm for aorta, >2 mm for the subclavian/axillary artery). Mural contrast enhancement was subjectively scored as 0 (no mural enhancement), 1 (mild mural enhancement), 2 (strong mural enhancement and/or perivascular enhancement) using static and dynamic T1w sequences pre and post contrast. Mural oedema was subjectively scored as 0 (no mural oedema), 1 (mild mural oedema), 2 (strong mural oedema) using T2w BLADE and diffusion-weighted sequences (Supplementary Table S2).

PET/CT image acquisition and assessment

PET/CT scanning was performed on a Siemens Biograph PET/CT mCT128 scanner (Siemens Healthcare, Erlangen, Germany). Patients were fasting for at least 6 hours before intravenous injection of 5 MBq FDG/kg body weight at median glycaemic levels below 10 mmol/L and scans were obtained 1 hour after injection as previously described (6). The PET/CT scans were assessed by an experienced board-certified nuclear medicine specialist (C.R., 17 years of experience) blinded to the clinical and complementary imaging results. The degree of FDG uptake was quantified using the maximum standardized uptake value (SUV) of the vessel divided by the mean SUV of the liver. Findings positive for vasculitis were defined as artery/liver SUV ratio >1 for the subclavian/axillary segment and >1.3 for the aorta as previously validated (5,6).

Ultrasound examination and assessment

Vascular ultrasound was done using EPIQ 7 duplex devices with a linear 12-3 MHz and 18-5 MHz transducer (both from Philips, Best, The Netherlands) (17). An experienced angiologist (M.A.) blinded to the clinical data, MRI and PET/CT results evaluated all ultrasound images. LVV was defined as circumferential homogenous hypoechoic wall thickening, well-delineated towards the luminal side and without arteriosclerotic lesions (18).

Comparison of MRI with PET/CT and ultrasound

Due to varying anatomical definitions in the different imaging modalities, we combined the analysis of the subclavian and axillary segments into one segment per side (axillary artery) to improve comparability between the imaging methods. The axillary segments are commonly affected in LV-GCA and are accessible for all three imaging modalities (19). Additionally, we compared vascular findings of the thoracic aorta between MRI and PET/CT in the same patients.

Statistical analysis

Continuous variables are expressed as medians with interquartile ranges (IQR). Categorical variables are presented as numbers with percentages. All statistical analyses were performed in R version 4.1.1 (2021-08-10) (20).

Results

Study population

Twelve patients (7 females, 58%; median age 72.1 years, IQR 65.5–74.2) with newly diagnosed LV-GCA were included in the study. Median erythrocyte sedimentation rate was 64 mm/h (IQR 39.5–78.3) and median C-reactive protein was 40.6 (IQR 12.5–101.7). The most common symptoms were headache, jaw claudication and polymyalgia (42% each). MRI was performed at a median of 16 days (IQR 6.8–29.8), PET/CT at a median of 7 days (IQR 3.8–11.3), and ultrasound at a median of 4 days (IQR 2.0–12.3) after glucocorticoid treatment initiation.

MRI findings compared to PET/CT and ultrasound in the axillary segments

MRI showed mural thickening in 9/24 (37.5%) segments. Of these, 8 segments had additional mural oedema of which 3 segments also showed additional contrast agent enhancement. Eight of 9 thickened segments on MRI were classified as vasculitis on PET/CT. Only one segment showed thickening and oedema on MRI, but without corresponding findings in PET/CT (Patient 10, right segment, SUV artery/liver ratio = 0.9 [cut-off > 1]). Two of 9 segments with thickening on MRI had congruent vasculitic findings on ultrasound (one with a negative PET/CT result), but 7 segments with thickening on MRI were negative on ultrasound.

Five segments were classified as vasculitis on PET/CT and ultrasound, and another 3 segments on ultrasound only, which were normal on MRI. In all of these patients, MRI was performed more than 6 days after the start of prednisone treatment (Table 1).

MRI findings compared to PET/CT in the thoracic aorta

Four of 12 patients showed mural thickening with concomitant oedema and contrast enhancement of the thoracic aorta on MRI. Of these, three patients had congruent vasculitic findings on PET/CT. Only one patient with mural thickening, oedema and enhancement on MRI was not classified as vasculitis by PET/CT but had a SUV artery/liver ratio of 1.21 which is just below the cut-off of 1.3 for vasculitis (Patient 10). One patient had isolated thickening on MRI of the thoracic aorta, which was negative on the corresponding PET/CT (Patient 6 in Table 1). Figure 1 shows PET/CT and MRI findings of patient 3.

Discussion

To date, there are no standardised criteria for the diagnosis of LV-GCA by MRI (1). We here aimed to identify parameters on MRI corresponding to vasculitis by comparing MRI to PET/CT and ultrasound on a segment level for the most often in LV-GCA involved arteries; the axillary segment as well as the thoracic aorta.

The presence of oedematous wall thickening on MRI corresponded to vasculitic findings on PET/CT, whereas isolated vessel wall thickening not related to oedema was found in two segments only on MRI, one of which did not show any FDG uptake on PET/CT. Non-oedematous wall thickening has been shown to be an unspecific finding that may be seen in overt atherosclerosis (21) or in patients with cardiovascular risk factors as surrogate marker of subclinical arteriosclerosis (22). Contrast enhancement was less frequently found in the axillary segment and did not increase the yield of pathological findings on MRI in our study. If contrast agents could be avoided, the availability of MRI for patients with allergies and renal insufficiency would increase and the examination time would be reduced.

We found a high accordance of oedema on MRI with FDG uptake on PET/CT, but not with ultrasound. Only 1/8 segments classified as vasculitis on MRI and PET/CT were positive on

ultrasound. This suggests that MRI and PET/CT on the one hand, and ultrasound on the other, visualise different vessel wall pathologies. We have previously shown similar findings for PET/CT compared to ultrasound (23).

MRI rarely showed vasculitic changes if glucocorticoids were given for longer than a week, consistent with a previously published study (11). Similarly, sensitivity of PET/CT has been described to decrease with duration of glucocorticoid treatment (5), while ultrasound pathologies in the larger arteries seem to be less affected by steroid treatment (15,17). This may explain the large discrepancy of subclavian/axillary segments being normal on MRI but showing vasculitis on ultrasound in patients having received more than 6 days of steroid treatment. Furthermore, the lower spatial resolution of MRI may have influenced its sensitivity in comparison with ultrasound. However, it remains unclear why ultrasound did not show vasculitis in the majority of segments that were positive on both, PET/CT and MRI. Due to the study inclusion criteria (patients with LV-GCA in PET/CT at diagnosis of GCA) we cannot draw conclusions about the diagnostic accuracy of the different techniques.

This study has limitations: first, the small number of included patients. Second, glucocorticoid treatment started before imaging, which was on average the longest before MRI. This may have had disparate effects on the sensitivities of the different imaging modalities.

In conclusion, vessel wall thickening due to oedema on MRI was the essential feature of active vasculitis in direct comparison to PET/CT, while contrast agent enhancement appeared to be redundant and was seen less frequent than oedema. Pathologic findings on MRI had a low agreement with vasculitic ultrasound findings suggesting that the presentation of vasculitis as seen on ultrasound is different from the vasculitic features seen on MRI imaging.

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Conflict of interest

AH is supported by a grant from the Swiss Foundation for Research on Muscle Diseases (FSRMM). DK received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, Janssen, Novartis, Pfizer, Roche, and Eli Lilly and support for attending meetings and/or travel from Janssen. DS received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, educational events, or advisory board from Bayer, Pfizer, Bristol-Myers-Squibb, Daiichi-Sankyo, Sanofi, Philips and Bauerfeind AG. TD received payment or honoraria for lectures and advisory boards from Novartis and CSL and holds IIT grants from Novartis and Abbvie. All other authors have no competing interests.

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Contributors

All authors gave substantial contributions to study conception or design of the work, acquisition of data, analysis and/or interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version of the article to be published.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Data availability

The data used and analysed during this study are available from the corresponding author upon reasonable request.

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Table and figure legends

Table 1: Imaging findings and glucocorticoid treatment per patient in the axillary arteries and thoracic aorta.

Figure 1: Findings rated positive for large vessel vasculitis in the descending thoracic aorta on MRI and FDG-PET/CT: MRI shows oedema on both T2w fat-suppressed (A) and low b-value diffusion weighted sequences (B) accompanied by wall thickening and gadolinium enhancement on post contrast T1w GRASP (C). PET shows increased FDG uptake in the identical position (D). Figure (E) is a PET/MRI image fusion of the corresponding images (B) and (D) (Image fusion with Siemens SyngoVia version VB40). Red arrows highlight vessel wall oedema, contrast enhancement and increased FDG uptake, respectively.

Abbreviations: FDG=[18F]fluorodeoxyglucose; MRI=magnetic resonance imaging; PET/CT=FDG positron emission tomography/computed tomography; GRASP = Golden-angle RAdial Sparse Parallel (MRI).

Table 1: Imaging findings and duration of glucocorticoid treatment per patient in the axillary arteries and thoracic aorta.

	Axillary artery						Thoracic aorta				GC treatment days before imaging		
Patient	**Side**	**US**	**PET/CT**	**Mural MRI findings**			**PET/CT**	**Mural MRI findings**			**US**	**PET/CT**	**MRI**
				Thickening	Oedema	C-Enhancement		Thickening	Oedema	C-Enhancement			
1	R L	- -	- pos	- mild	- mild	- mild	pos	strong	strong	strong	0	0	0
2	R L	- -	pos pos	- mild	- -	- -	pos	mild	mild	mild	0	0	0
3	R L	pos -	pos pos	mild mild	mild mild	- -	pos	mild	mild	mild	0	0	4
4	R L	- -	pos pos	mild mild	mild mild	- -	pos	-	-	-	1	18	4
5	R L	- -	pos pos	mild mild	strong strong	mild mild	-	-	-	-	2	4	6
6	R L	pos pos	- -	- -	- -	- -	-	mild	-	-	3	3	9
7	R L	pos pos	pos pos	- -	- -	- -	-	-	-	-	5	8	16
8	R L	N/A -	- -	- -	- -	- -	-	-	-	-	12	9	16
9	R L	N/A pos	- pos	- -	- -	- -	-	-	-	-	29	0	23
10	R L	pos pos	- -	mild -	mild -	- -	-	strong	strong	mild	0	1	32
11	R L	pos pos	pos pos	- -	- -	- -	pos	-	-	-	2	6	34
12	R L	- -	- -	- -	- -	- -	-	-	-	-	15	30	41

Abbreviations: GC=glucocorticoid; C-Enhancement= Contrast-Enhancement; MRI=magnetic resonance imaging; PET/CT= [^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography; US=ultrasound; pos = positive; - = negative; N/A=not available.

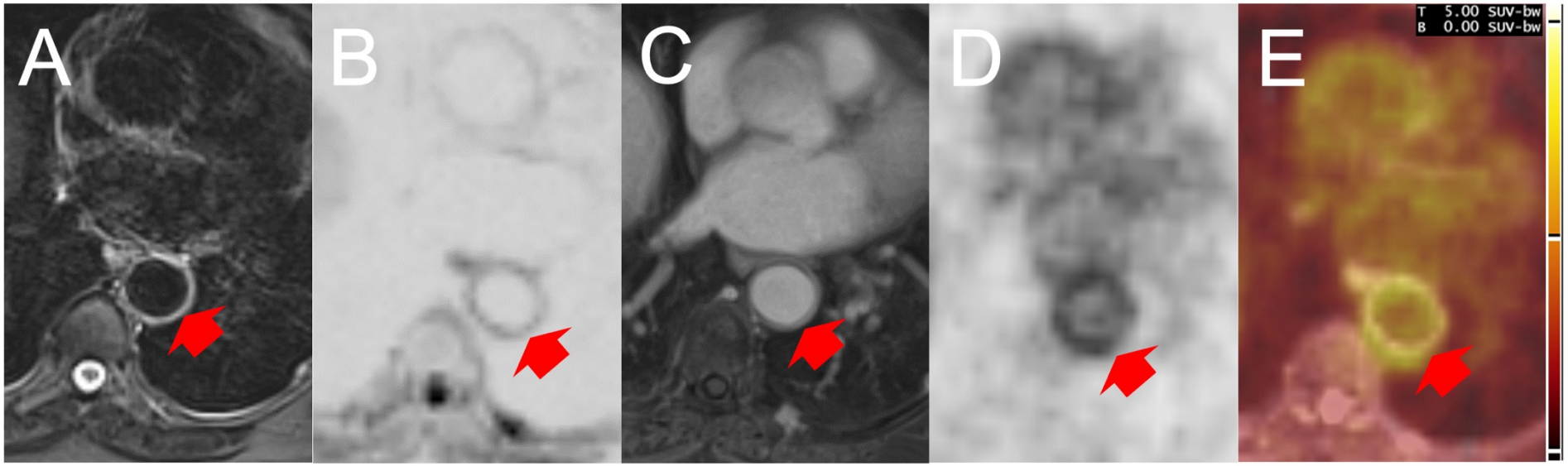

Figure 1: Findings rated positive for large vessel vasculitis in the descending aorta on MRI and FDG-PET/CT: MRI shows oedema on both T2w fat-suppressed (A) and low b-value diffusion weighted sequences (B) accompanied by wall thickening and gadolinium enhancement on post contrast T1w GRASP (C). PET shows increased FDG uptake in the identical position (D). Figure (E) is a PET/MRI image fusion of the corresponding images (B) and (D) (Image fusion with Siemens SyngoVia version VB40). Red arrows highlight vessel wall oedema, contrast enhancement and increased FDG uptake, respectively.

Abbreviations: FDG=[18F]fluorodeoxyglucose; MRI=magnetic resonance imaging; PET/CT=FDG positron emission tomography/computed tomography; GRASP = Golden-angle RAdial Sparse Parallel (MRI).

Supplementary Material

Supplementary Table S1: Patient characteristics at diagnosis.	
Characteristics	**Patients (N=12)**
Age, years	72.1 (65.5–74.2)
Female	7 (58%)
ESR, mm/h	64.0 (39.5–78.3)
CRP, mg/dl	40.6 (12.5–101.7)
Leukocytes, G/l	9.9 (7.1–11.5)
Thrombocytes, G/l	327.0 (263.2–462.8)
Fever	2 (17%)
Headache	5 (42%)
Jaw claudication	5 (42%)
Scalp tenderness	3 (25%)
Polymyalgic symptoms	5 (42%)
Tenderness of the temporal artery	3 (25%)
Stroke	1 (8%)
Vision loss	1 (8%)
Hypertension	3 (25%)
Diabetes mellitus	2 (17%)
Dyslipidaemia	5 (42%)
Smoking	6 (50%)
Coronary artery disease	3 (25%)
Cerebrovascular disease	2 (16%)
Peripheral artery disease	1 (8%)
Abbreviations: CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; Categorical variables are shown as numbers with percentages and continuous variables as medians with interquartile ranges.	

Supplementary Table S2: MRI sequence protocol.							
#	**Name**	**Orientation**	**TR (ms)**	**TE (ms)**	**Matrix**	**FOV (mm^2)**	**Respiratory motion compensation**
1	T2w HASTE	Coronal	600	30	256 x 320	40 x 480	Breath hold
2	T2w HASTE	Transverse	500	30	240 x 320	380 x 380	Breath hold
3	bSSFP	Transverse	295	1.2	208 x 256	293 x 360	Breath hold
4	T2w BLADE	Transverse	6200	119	256 x 256	350 x 350	Respiratory triggering
5	T1w VIBE Dixon pre contrast	Transverse 3D	6.7	2.4/4.8	180 x 320	300 x 400	Breath hold
6	DW-EPI b50/800	Transverse	6760	60	112 x 140	344 x 430	Free breathing
7	GRASP dynamic	Transverse 3D	3.3	1.5	256 x 256	360 x 360	Free breathing
8	T1w VIBE Dixon post contrast	Transverse 3D	6.7	2.4/4.8	180 x 320	300 x 400	Breath hold
Abbreviations: BLADE=proprietary name for periodically rotated overlapping parallel lines with enhanced reconstruction (PROPELLER) in MRI systems from Siemens Healthcare; bSSFP=balanced Steady-State Free Precession; DW-EPI=Diffusion Weighted Echo Planar Imaging; FOV=field-of-view; GRASP= Golden-angle RAdial Sparse Parallel imaging; HASTE=Half-Fourier Acquisition Single-shot Turbo spin Echo imaging; VIBE=Volumetric Interpolated Breath-hold Examination.							

4.4 Manuscript IV: Imaging to predict relapses after treatment discontinuation in patients with large vessel giant cell arteritis – a cohort study

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Key words: giant cell arteritis, imaging, vasculitis, magnetic resonance imaging

Abstract

Objectives: To investigate the value of [^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) and magnetic resonance imaging (MRI) in predicting relapse after treatment discontinuation in patients with large-vessel giant cell arteritis (LV-GCA).

Methods: This study included patients with LV-GCA whose treatment was discontinued between 2018-2023. All patients underwent PET/CT and/or MRI at the time of treatment discontinuation in clinical remission. Imaging findings of the aorta and supraaortic vessels were compared between patients who relapsed within 4 months after treatment discontinuation and those who did not.

Results: Forty patients were included (median age 67.4 years, interquartile range (IQR) 60.8-74.0; 77.5% females). Eleven patients (27.5%) relapsed after treatment discontinuation (time to relapse 1.9 months, IQR 1.4-3.3). Patients who relapsed were comparable to those who remained in remission with respect to the presence of active vasculitis on MRI and/or PET/CT (54.5% vs. 58.6%, p=1.0), the number of segments with vasculitic findings on MRI (0, IQR 0.0-1.5, vs. 2, IQR 0.0-3.0, p=0.221) or the highest standardized uptake value artery/liver ratio on PET/CT (1.5, IQR 1.4-1.6, vs. 1.3, IQR 1.2-1.6, p=0.505). The median number of vasculitic segments on PET/CT was 2.5 (IQR 0.5-4.5) in those with vs. 0 (IQR 0.0-1.5, p=0.085) in those without relapse, and the modified PET vascular score (PETVAS) was 4.5 (IQR 0.75-8.25) vs. 0 (IQR 0.0-3.0, p=0.172).

Conclusion: PET/CT or MRI at treatment stop did not predict relapse and may not be suited to guide treatment decisions in patients with LV-GCA in remission.

Key messages

What is already known on this topic

- There is no established imaging biomarker for guiding the timing of treatment stop in patients with LV-GCA.

What this study adds

- More than half of LV-GCA patients in clinical remission show signs of active vessel wall inflammation on PET/CT and MRI.
- The presence or absence of vasculitic findings on PET/CT and/or MRI did not predict subsequent relapse after treatment stop.

How this study might affect research, practice or policy

- The role of PET/CT and/or MRI in guiding the decision of whether to stop or continue treatment in patients with LV-GCA seems limited.
- The relevance of vasculitic imaging findings in patients in clinical remission of GCA should be further studied.

Introduction

Imaging is needed to establish a diagnosis of large vessel giant cell arteritis (LV-GCA), which is characterized by inflammation of the aorta and its branches (1,2). Patients with GCA frequently relapse (3). Identifying patients at risk for relapse and clinical assessment of disease activity remains challenging (4). Normalised inflammatory markers and the absence of symptoms during maintenance therapy do not always indicate the absence of active inflammation and hence true remission (4). Therefore, the duration of steroid treatment is still debated and half of all patients relapse after stopping therapy (3,5,6). Disease activity assessment is even more complex in patients treated with tocilizumab, an interleukin-6 receptor alpha inhibitor, which directly suppresses C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), rendering these important parameters useless for assessing disease activity (7–9). How imaging findings of the large vessels change during treatment and how this relates to disease activity is not well studied. Reports on follow-up imaging in patients with GCA during clinical remission showed reduced but persistently increased [^{18}F]fluorodeoxyglucose (FDG) uptake on positron emission tomography/computed tomography (PET/CT) (10,11), signs of vasculitis on MRI (12), and persistent vessel wall thickening on ultrasound (13,14). The significance of these imaging findings remains unclear.

Conflicting results exist on the role of imaging to predict future relapse during ongoing treatment in patients with LV-GCA (10,15–18). Three studies performed PET or PET/CT early in the disease course but showed contradictory results concerning the ability of PET to predict subsequent relapses (10,16,18). Contrasting findings have also been reported by two studies investigating the predictive value of PET/CT in selected patients who had undergone PET/CT scans several years into the disease course during a period of clinical remission (15,17). These imaging studies selected patients who had undergone imaging at various stages of the disease and assessed the occurrence of relapse during ongoing treatment (15–17). Additionally, these

studies had heterogenous patient populations, including patients with Takayasu's arteritis (TAK) (15–17).

The decision of when to safely discontinue treatment in patients with clinically inactive disease is not based on solid evidence and biomarkers predicting outcome after treatment discontinuation are lacking (4). To what extent the decision to stop treatment can be guided by imaging remains an open question.

This study aimed to investigate the value of PET/CT and MRI performed at the end of treatment for predicting relapse in patients with LV-GCA.

Methods

Patients and setting

Large vessel imaging is routinely performed in our clinic in all patients with newly diagnosed GCA to assess potential extracranial large vessel involvement (4). This is a cohort study of patients with imaging-confirmed LV-GCA diagnosed at the University Hospital Basel between September 2011 and January 2022. We prospectively enrolled consecutive patients in clinical and serological remission and scheduled to discontinue treatment and undergo follow-up imaging between December 2020 and April 2023. Patients were followed up in our clinic for at least four months after treatment discontinuation. In addition, we retrospectively identified patients with LV-GCA from our local GCA cohort who had imaging performed during remission at treatment discontinuation and a well-documented follow-up of at least four months after that. A diagnosis of GCA was made if temporal artery biopsy was positive, if the 1990 criteria from the American College of Rheumatology (ACR) were met, or if at least 2 of 5 ACR criteria were fulfilled in combination with findings typical for vasculitis on imaging (19). LV-GCA was defined as the involvement of the aorta and/or carotid, vertebral, subclavian, axillary, and/or femoral arteries on imaging.

This study was approved by our local Ethics committee (EKNZ Project-ID 2019-02161, 'Basler Riesenzellarteriitis Kohorte' (BARK) EKNZ, #239/09) and was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Data collection and definitions

Data on patient demographics, clinical presentation, laboratory results and treatment at the time of GCA diagnosis and follow-up were retrieved from our local GCA cohort and by medical chart review. Remission was defined as the normalisation of inflammatory markers and the absence of any clinical symptoms of GCA (20). Relapse was defined as the reoccurrence of symptoms directly attributable to GCA or an increase in inflammatory markers that could not otherwise be explained and requiring the reinstitution of immunosuppressive therapy (20). Per the European Alliance of Associations for Rheumatology (EULAR) consensus definitions, we defined major relapse as the occurrence of clinical signs of ischemia (jaw claudication, visual impairment, vision loss, stroke, limb claudication), as well as aortic damage (dilation, stenosis, dissection) and minor relapse as the occurrence of signs or symptoms of active disease not fulfilling the criteria for a major relapse (recurrence of headache, polymyalgia or elevation of inflammatory markers only) (20).

PET/CT image acquisition and assessment

All patients underwent PET/CT scanning on a Siemens Biograph PET/CT mCT128 scanner (Siemens Healthcare, Erlangen, Germany). Patients were fasting for at least 6 hours before intravenous injection of 5 MBq FDG/kg body weight at median glycaemic levels below 10 mmol/L and scans were obtained 1 hour after injection as previously described (21). The PET/CT scans were assessed by an experienced board-certified nuclear medicine specialist (C.R., 17 years of experience) blinded to the clinical and complementary MRI findings. The degree of FDG uptake within the following vessel regions was assessed using the maximum standardized uptake value (SUV_{max}) of the vessel divided by the mean SUV (SUV_{mean}) of the

liver: the superficial temporal arteries (trunk, parietal, and frontal branches), the common, internal, and external carotid arteries, the vertebral, subclavian and axillary arteries, thoracic and abdominal aorta, and femoral arteries. To assess the SUV_{max}, vessels with visually suspect FDG-uptake were analysed. In the suspect section of the according vessels, SUV_{max} was measured within a volume of interest (VOI) while sparing structures adjacent to the vessel by careful visual inspection and adaptation of the VOI size and position, if needed. SUV_{mean} liver was measured within a VOI in the right liver lobe, sparing areas of elevated or reduced liver uptake and structures such as large vessels by inspection of the co-registered CT images. For SUV measurement, Siemens SyngoVia software (Siemens, Erlangen, Germany) was used. Findings positive for vasculitis were defined as SUV_{max} artery/liver ratio >1 for the supra-aortic region and >1.3 for the aorta and femoral region (21,22). The PET/CT scan was considered positive for vasculitis, if at least one vessel segment had an SUV_{max} artery/liver ratio above cut-off. To assess the overall burden of vasculitic findings on PET/CT, six segments (carotids, subclavian arteries, thoracic aorta, abdominal aorta) were graded according to their SUV_{max} artery/liver ratio as 0 = no uptake, 1 = less than liver, 2 = equal to liver, 3 = greater than liver. A modified PET/CT vascular (PETVAS) score of 0–18 was calculated by summing the scores of the six segments (15).

MRI acquisition and assessment

MRI examinations were performed on a 1.5 T clinical MRI system (Magnetom Avanto fit, Siemens Healthineers, Erlangen, Germany). For contrast-enhanced imaging, a Gadolinium-based contrast agent (Gadobutrol (Gadovist ®), Bayer AG, Leverkusen, Germany) was applied in the standard dose of 0,1 mmol Gd/kg body weight. MRI findings (mural thickening, contrast agent enhancement, and mural oedema) were assessed by a board-certified radiologist (G.S., 8 years of experience), blinded to clinical data and PET/CT scans. The subclavian arteries, the common carotid arteries and the thoracic aorta (ascending and descending aorta, aortic arch)

were analysed with and without Gadolinium contrast agent. Mural thickening was defined as thickening ≥2 mm for the aorta, and ≥1 mm for its branches. The presence or absence of contrast agent enhancement was subjectively assessed using static and dynamic T1w sequences pre and post contrast. The presence or absence of mural oedema was subjectively assessed using fat-suppressed T2w fast spin echo and diffusion-weighted sequences. A segment showing mural thickening with concomitant oedema and/or mural contrast enhancement was considered to represent vasculitis. Isolated mural thickening was not considered a sign of vasculitis. The MRI was categorized as positive for vasculitis, if at least one segment met the predefined criteria for vasculitis.

Statistical analysis

This was an exploratory study testing a range of quantitative and qualitative parameters detected in imaging for their ability to identify patients who will experience future relapse after treatment discontinuation. The primary endpoint of our study was the occurrence of relapse within four months of treatment discontinuation. Patients having experienced a relapse after treatment discontinuation were compared to patients who did not, concerning 1) the presence of vasculitic findings on PET/CT and/or MRI (vasculitis vs. normal imaging findings) at the time of treatment discontinuation; 2) the extent of vasculitic findings on PET/CT or MRI (number of vasculitic segments); 3) the intensity of FDG uptake on PET/CT (highest SUV_{max}) as well as the sum of SUV_{max} artery/liver ratios of all vessels in the subgroup of patients who had FDG uptake on PET/CT in at least one vessel and 4) the severity of vascular involvement on PET/CT using the modified PETVAS score. In the subgroup of patients who had a PET/CT performed at diagnosis and at treatment discontinuation, we examined the change in the modified PETVAS between diagnosis and treatment stop and compared it between relapsing and non-relapsing patients. Continuous variables were expressed as mean and standard deviation (SD) or as the median and interquartile range (IQR) and categorical variables as numbers with

percentages. Differences between distributions of continuous variables were compared using a two-tailed student's t-test or Mann-Whitney U test, as appropriate. Differences between categorical variables were analysed using the chi-square test or Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant. All statistical analyses were performed in R version 4.1.1 (2021-08-10) (23).

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Results

Study cohort

Between December 2020 and April 2023, 69 patients with LV-GCA were treated at the University Hospital Basel. During this period, 33 patients stopped their treatment and were consecutively included in our study. Additionally, seven patients who withdrew treatment between January 2018 and November 2020 and had imaging performed were retrospectively identified, resulting in a total of 40 patients included in the study (Figure 1). The median age at GCA diagnosis was 67.4 (IQR 60.8–74.0 years), and 31 patients (77.5%) were females. Characteristics of the patients at GCA diagnosis are shown in Table 1.

Time of treatment discontinuation and subsequent relapses

The median disease duration from diagnosis to treatment discontinuation was 20.3 months (IQR 13.1–36.4). Twelve patients had a PET/CT scan, 15 had an MRI, and 13 underwent both imaging examinations at treatment discontinuation.

Thirteen patients had discontinued treatment a median of 12 days prior to the PET/CT (IQR 6.0–15.0). On the day of the PET/CT scan, two patients were taking prednisone <5 mg and 10

patients received tocilizumab. The median time from the PET/CT scan to 'the last day of treatment' or to 'the last tocilizumab injection' was 9 days (IQR 6.8–29.8).

Eighteen patients had stopped treatment a median of 27.5 days before MRI (IQR 11.5–34.0). On the day of the MRI, 3 patients had <5 mg of prednisone, one had 7.5 mg of prednisone, five received tocilizumab and one was on methotrexate. In these patients, treatment was discontinued a median of 5.5 days after MRI (IQR 1.5–19.5).

Eleven patients (27.5%) experienced a relapse a median of 1.9 months after treatment discontinuation (IQR 1.4–3.3 months). Nine relapses were minor (81.8%), and two patients (18.2%) had a major relapse with jaw claudication. The most common manifestations of relapse were an increase in inflammatory parameters and/or polymyalgic symptoms.

Presence of vasculitic imaging findings in at least one vessel segment

Twenty-three of 40 patients (57.5%) had vasculitic findings in at least one vessel segment on either PET/CT and/or MRI at treatment stop. Vasculitic findings were found in 6 of 11 patients (54.5%) who relapsed and in 17 of 29 patients (58.6%) who remained in remission (p=1) (Table 2). Five patients who experienced a relapse had normal imaging findings and 17 patients with persistent findings did not relapse (Figure 2).

Four of six (66.7%) patients who relapsed showed a pathological PET/CT compared to 8/19 (42.1%) patients who remained in remission (p=0.378). The presence of vasculitic findings on MRI did not differ between relapsing and non-relapsing patients (28.6% vs. 57.1%, p=0.385). Patients treated with tocilizumab showed vasculitic findings in 52% compared to 66.7% of patients on glucocorticoids or methotrexate (p=0.512) (Supplementary Table S1).

Number of vasculitic vessel segments on imaging to predict future relapse

There was no statistically significant difference in the median number of segments with vasculitic findings between relapsing and non-relapsing patients, neither on PET/CT (2.5 segments, IQR 0.5–4.5, vs. 0.0 segments, IQR 0.0–1.5, p=0.085), nor on MRI (median of 0

segments, IQR 0.0–1.5, vs. 2 segments, IQR 0.0–3.0, p=0.221). Neither the number of arteries with mural contrast agent enhancement (0 segments IQR 0.0–1.0, vs. 0 segments IQR 0.0–1.0, p=0.877), nor with mural oedema (0 segments IQR 0.0–1.5, vs. 2 segments IQR 0.0–3.0, p=0.293) was significantly different between relapsing and non-relapsing patients on MRI (Table 3).

SUV_{max} artery/liver ratio to predict future relapse

Visible FDG uptake on PET/CT was found in 16 of 25 patients. In these, the highest SUV_{max} artery/liver ratio per patient did not differ between patients who relapsed (N=4) and those who did not (N=12) (1.5, IQR 1.4–1.6, vs. 1.3, IQR 1.2–1.6, p=0.505) (Figure 3). The sum of all SUV_{max} ratios per patient did not differ between relapsing and non-relapsing patients (5.4, IQR 3.6–7.3, vs. 2.5, IQR 1.4–3.5, p=0.08).

Modified PETVAS to predict future relapse

The modified PETVAS score did not differentiate between patients with and without relapse (median score of 4.5, IQR 0.75–8.25, vs. 0, IQR 0.0–3.0, p = 0.172).

Overall, 22 patients had a PET/CT performed at diagnosis and at treatment discontinuation. The modified PETVAS decreased from diagnosis to treatment discontinuation in patients who relapsed and those who remained in remission (Figure 4). There was no statistically significant difference in the decrease of the modified PETVAS between patients with and without relapses (p=0.312) (Table 4).

Discussion

None of the tested qualitative or quantitative PET/CT or MRI parameters in this cohort study could predict relapse after treatment discontinuation in patients with LV-GCA. Neither the presence of signs of active vessel wall inflammation, nor the extent of vasculitic findings on

MRI, the intensity of FDG uptake, nor the modified PETVAS and its change from baseline to the end of treatment identified patients who relapsed. The number of segments with vasculitic findings on PET/CT and the sum of all SUV_{max} artery/liver ratios showed a slight tendency to be higher in patients who relapsed; however, this did not reach statistical significance.

To our knowledge, this is the first study prospectively performing PET/CT or MRI at the time of treatment discontinuation to investigate their usefulness in predicting subsequent relapse in patients with LV-GCA. One study focusing on MRI only systematically performed MRI at the cessation of tocilizumab treatment in 17 patients (24). Consistent with our findings, the presence or absence of vessel wall enhancement on MRI was not related to future relapse (24). Furthermore, in our study, the number of segments with vasculitic findings on MRI was not associated with subsequent relapses. Therefore, an MRI performed at treatment stop seems unreliable in predicting subsequent relapses.

We found a slight tendency towards a higher number of positive PET/CT segments and a higher sum of all SUV_{max} artery/liver ratios in relapsing patients. This suggests the hypothesis that the assessment of the extent of vascular involvement combined with the intensity of arterial FDG uptake may be, to some degree, able to predict relapse after treatment stop in contrast to the mere presence or absence of vasculitic findings on PET/CT or the highest SUV_{max} artery/liver ratio per patient. This hypothesis is somewhat contradicted by the modified PETVAS, which was used to assess the global severity of vascular inflammation but whose performance in predicting subsequent relapses was low in our study.

In the study by Grayson et al., a higher PETVAS was associated with future clinical relapse (15). However, they assessed the ability of PETVAS to predict relapse during ongoing treatment, but not specifically at treatment stop and included patients with GCA and patients with TAK (15). In contrast, in the study by Galli et al., PETVAS was not associated with

subsequent relapse during ongoing treatment in retrospectively selected patients with GCA or TAK (17).

More than half of our patients had signs that are considered to represent active vasculitis in at least one vessel segment at treatment discontinuation. This aligns with previous studies that identified signs of vasculitis on PET/CT or MRI in GCA patients in clinical remission during ongoing treatment (10,12,15). In the study by Adler et al., all patients in long-lasting remission after treatment discontinuation showed persistent signals of vessel wall enhancement on MRI (24). Whether these vasculitic imaging findings reflect subclinical vasculitis or vascular remodelling remains controversial due to the lack of histopathological comparisons (4,12,15,25). In a recent study, the histopathological evaluation of the aorta of patients with GCA who had aortic aneurysm or dissection surgery revealed active aortitis in most patients, despite being in clinical remission for several years since diagnosis (26). These results support the hypothesis that vasculitic imaging findings could indeed represent active inflammation and that chronic, smouldering inflammation may contribute to the development of aortic aneurysms and dissection (26). It thus remains unclear how patients who are scheduled to stop treatment but have vasculitic imaging findings should be managed. Long-term prospective studies are needed to assess whether patients with residual imaging findings are at a higher risk for developing future aneurysms or vascular dissections.

As most patients in our cohort presented with polymyalgia rheumatica (PMR) symptoms and elevated inflammatory markers at relapse after treatment stop, we investigated whether FDG uptake typical of PMR on PET/CT could predict relapse. However, these findings did not discriminate between patients with and without future relapse (data not shown).

This study has several limitations. The patient cohort was heterogenous, including mostly prospectively but a small number of retrospectively recruited patients. Treatment was left to the discretion of the treating physician, depending on the individual response to therapy.

Furthermore, due to capacity constraints during the Covid-19 pandemic it was not always possible to perform both PET/CT and MRI in all prospectively recruited patients at treatment discontinuation. Lastly, our sample size was small, increasing the probability of a type II error. Strengths of our study include that all patients had imaging-confirmed large-vessel involvement at diagnosis, and all imaging studies were systematically performed during clinical remission at the time of treatment discontinuation.

In conclusion, neither findings on PET/CT nor MRI performed at the end of treatment and during clinical and laboratory remission predicted subsequent relapse in patients with LV-GCA. Imaging does not appear to be a valuable addition to clinical and laboratory assessment in determining the duration of therapy in patients with LV-GCA. The significance of persistent signs of vasculitis on imaging for developing aortic aneurysms or dissections needs to be studied prospectively.

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Conflict of interest

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Contributors

All authors gave substantial contributions to study conception or design of the work, acquisition of data, analysis and/or interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version of the article to be published.

Data availability

The data used and analysed during this study are available from the corresponding author upon reasonable request.

Ethics

This study was approved by the local Ethics committee (EKNZ, Project-ID 2019-02161; 'Basler Riesenzellarteriitis Kohorte' (BARK) EKNZ, #239/09).

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Table and figure legends

Table 1: Patient characteristics at diagnosis.

Table 2: Presence of vasculitic imaging findings in at least one segment in patients with and without relapse after treatment withdrawal.

Table 3: Median number of segments with vasculitic imaging findings in patients with and without relapse after treatment withdrawal.

Table 4: Change of the modified PETVAS from diagnosis to treatment stop.

Figure 1: Flowchart of patient selection.

Abbreviations: GP=general practitioner; LV-GCA=large-vessel giant cell arteritis; RCT=randomized controlled trial.

Figure 2: Imaging examples of a patient who remained in remission despite vasculitic findings in the thoracic aorta on MRI and PET/CT: MRI shows vessel wall oedema on low b-value diffusion weighted sequences (A) and vessel wall thickening and enhancement on T1w post Gadolinium (B). PET/CT shows increased FDG uptake in the aortic arch (C). Red arrows highlight vessel wall oedema, contrast enhancement and increased FDG uptake, respectively.

Abbreviations: FDG=[18F]fluorodeoxyglucose; MRI=magnetic resonance imaging; PET/CT=FDG positron emission tomography/computed tomography.

Figure 3: Comparison of the highest SUV_{max} artery/liver ratio between patients who remained in remission (N=12) and patients who relapsed (N=4) after treatment discontinuation.

Figure 4. Change in modified PETVAS for each patient from diagnosis to treatment stop.

Abbreviation: PETVAS= positron emission tomography vascular activity score.

Table 1: Patient characteristics at diagnosis.			
	No relapse after treatment withdrawal (N=29)	**Relapse after treatment withdrawal (N=11)**	**p-value**
Age, years	67.8 (60.9–75.1)	65.1 (60.6–73.1)	0.586
Female	22 (75.9)	9 (81.8)	1
ESR, mm/h	53 (29.0–78.3), N=26	42 (40.5–80.0)	0.536
CRP, mg/dl	45.2 (17.0–81.7), N=28	37.5 (21.5–95.2)	0.732
Leukocytes, G/l	9.6 (7.0-10.8), N=28	10.0 (6.4–10.4)	0.7401
Fever	6 (20.7)	1 (9.1)	0.65
Headache	13 (44.8)	7 (63.6)	0.48
Jaw claudication	8 (27.6)	5 (45.5)	0.451
Scalp tenderness	5 (17.2)	5 (45.5)	0.103
Polymyalgic symptoms	9 (31.0)	6 (54.5)	0.273
Tenderness of the temporal artery	6 (20.7)	4/10 (40.0)	0.244
Stroke	3 (10.3)	1 (9.1)	1.0
Permanent vision loss	2 (6.9)	0 (0.0)	1.0
Relapse during treatment	21 (72.4)	5 (45.5)	0.147
Time to treatment stop, months	20.3 (15.0–31.7)	12.1 (11.1–60.2)	0.633
Treated with tocilizumab	20 (69.0)	5 (45.5)	0.273
Hypertension	12 (41.4)	6 (54.5)	0.498
Diabetes	3 (10.3)	2 (18.2)	0.603
Dyslipidaemia	8 (27.6)	5 (45.5)	0.451
Smoking	15/27 (55.6)	6 (54.5)	1.0
Coronary artery disease	3 (10.3)	0 (0.0)	0.548
Cerebrovascular disease	5 (17.2)	1 (9.1)	1.0
Peripheral artery disease	1 (3.4)	0 (0.0)	1.0
Categorical variables are shown as N (%) and continuous variables as medians with interquartile ranges (IQR). Abbreviations: CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; GCA=giant cell arteritis; PMR=polymyalgia rheumatica.			

Table 2: Presence of vasculitic imaging findings in at least one segment in patients with and without relapse after treatment withdrawal.

Overall imaging* (N=40)	**No relapse (N=29)**	**Relapse (N=11)**	**p-value**
Presence of vasculitic findings	17 (58.6)	6 (54.5)	1
PET/CT (N=25)	**No relapse (N=19)**	**Relapse (N=6)**	**p-value**
Presence of vasculitic findings	8 (42.1)	4 (66.7)	0.378
MRI (N=28)	**No relapse (N=21)**	**Relapse (N=7)**	**p-value**
Presence of vasculitic findings	12 (57.1)	2 (28.6)	0.385

*Vasculitic findings on either PET/CT and/or MRI. Variables are shown as N (%). Abbreviations: MRI=magnetic resonance imaging; PET/CT=[18F]fluorodeoxyglucose positron emission tomography/computed tomography.

Table 3: Median number of segments with vasculitic imaging findings in patients with and without relapse after treatment withdrawal.

PET/CT	**No relapse (N=19)**	**Relapse (N=6)**	**p-value**
Number of segments with vasculitic findings on PET/CT	0.0 (0.0–1.5)	2.5 (0.5–4.5)	0.085
MRI	**No relapse (N=21)**	**Relapse (N=7)**	**p-value**
Number of segments with vasculitic findings on MRI*	2.0 (0.0–3.0)	0.0 (0.0–1.5)	0.221
Number of segments with mural enhancement	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.877
Number of segments with mural oedema	2.0 (0.0–3.0)	0.0 (0.0–1.5)	0.293

Variables are shown as medians with interquartile ranges (IQR). Abbreviations: PET/CT=[18F] fluorodeoxyglucose positron emission tomography/computed tomography; MRI=magnetic resonance imaging.

*Segments with mural thickening and concomitant enhancement and/or oedema.

Table 4: Change of the modified PETVAS from diagnosis to treatment stop.			
	No Relapse (N=17)	**Relapse (N=5)**	**p-value**
Modified PEVAS at diagnosis	9 (0.0–15.0)	0 (0.0–12.0)	0.625
Modified PETVAS at treatment stop	3 (0.0–3.0)	3 (0.0–9.0)	0.428
Change of the modified PETVAS	-5.0 (-10.0–0.0)	0.0 (-6.0–3.0)	0.311
Data are shown as medians and interquartile ranges (IQR). Abbreviations: PET/CT=[18F]fluorodeoxyglucose positron emission tomography/computed tomography; PETVAS= positron emission tomography vascular activity score SUV_{max}=maximum standardized uptake value.			

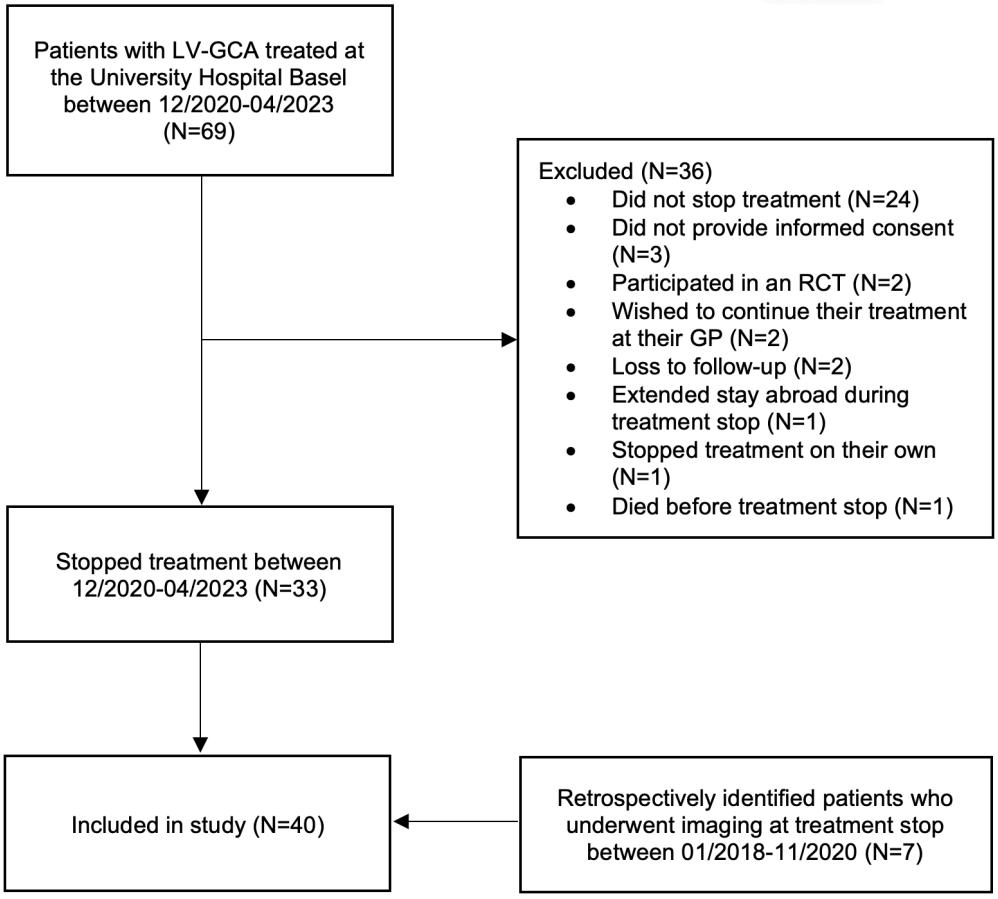

Figure 1. Flowchart of patient selection.

Abbreviations: GP=general practitioner; LV-GCA=large-vessel giant cell arteritis; RCT=randomized controlled trial.

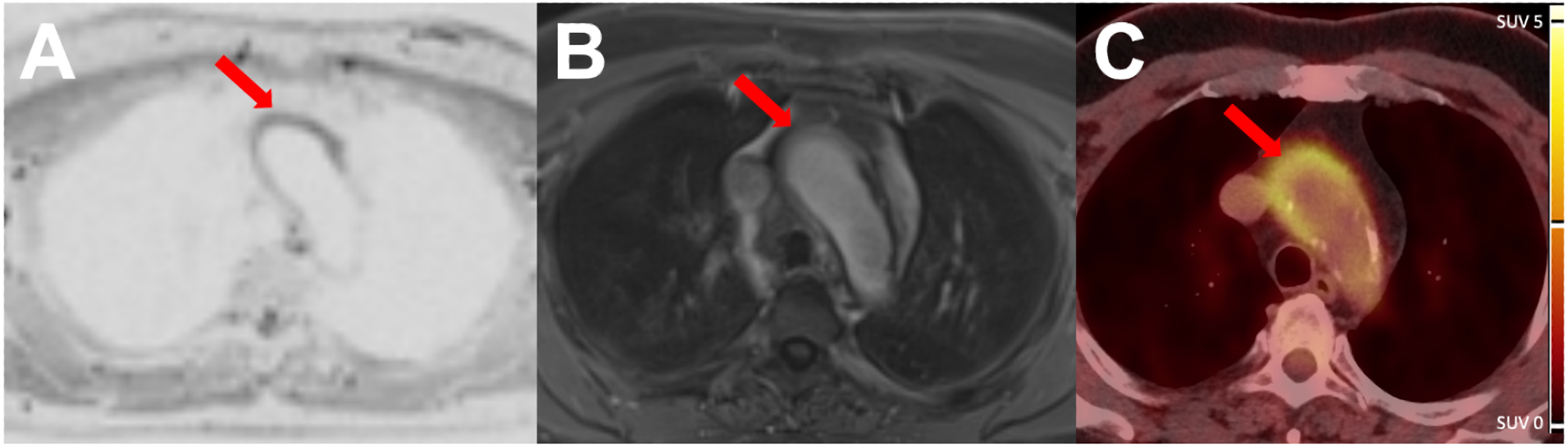

Figure 2: Imaging examples of a patient who remained in remission despite vasculitic findings in the thoracic aorta on MRI and PET/CT: MRI shows vessel wall oedema on low b-value diffusion weighted sequences (A) and vessel wall thickening and enhancement on T1w post Gadolinium (B). PET/CT shows increased FDG uptake in the aortic arch (C). Red arrows highlight vessel wall oedema, contrast enhancement and increased FDG uptake, respectively.

Abbreviations: FDG=[18F]fluorodeoxyglucose; MRI=magnetic resonance imaging; PET/CT=FDG positron emission tomography/computed tomography.

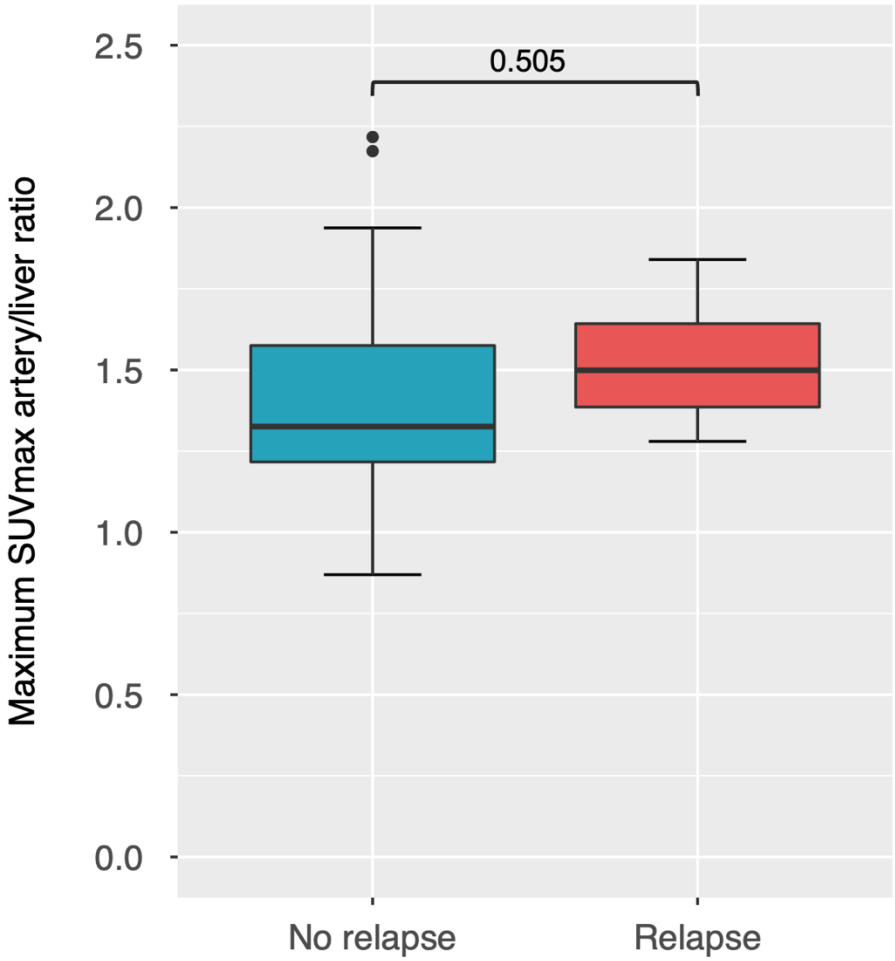

Figure 3: Comparison of the highest SUV_{max} artery/liver ratio between patients who remained in remission (N=12) and patients who relapsed (N=4) after treatment discontinuation.

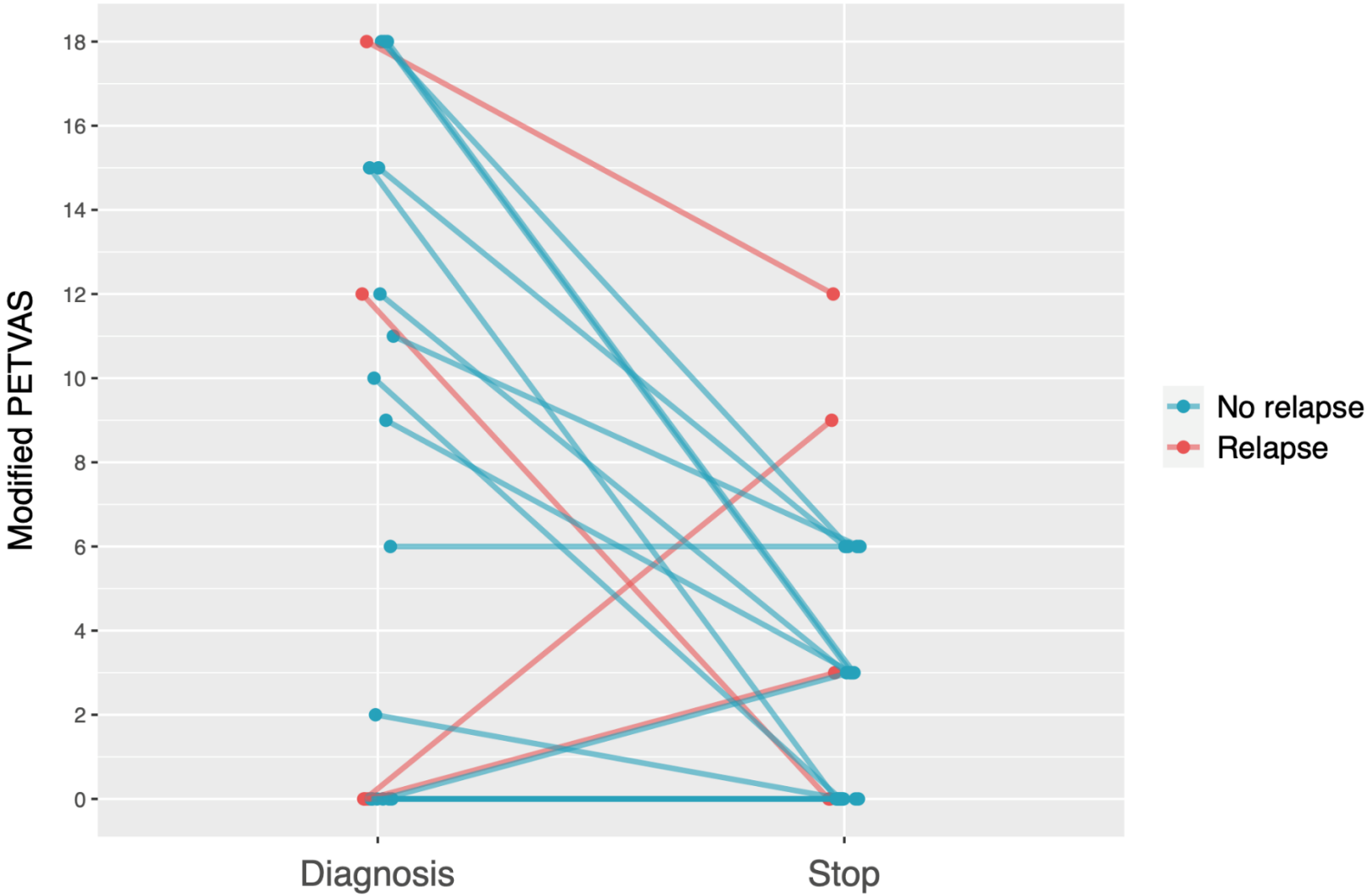

Figure 4. Change in modified PETVAS for each patient from diagnosis to treatment stop.

Abbreviation: PETVAS= positron emission tomography vascular activity score.

Supplementary Material

Supplementary Table S1: Presence of vasculitic imaging findings in any segment in patients treated with tocilizumab and patients treated without tocilizumab.

Overall imaging* (N=40)	**No TCZ (N=15)**	**TCZ (N=25)**	**p-value**
Presence of vasculitic findings	10 (66.7)	13 (52)	0.512
PET/CT (N=25)	**No TCZ (N=9)**	**TCZ (N=16)**	**p-value**
Presence of vasculitic findings	5 (55.6)	7 (43.8)	0.688
MRI (N=28)	**No TCZ (N=10)**	**TCZ (N=18)**	**p-value**
Presence of vasculitic findings	6 (60.0)	8 (44.4)	0.695

*Vasculitic findings on either PET/CT and/or MRI. Variables are shown as N (%). Abbreviations: MRI=magnetic resonance imaging; PET/CT=[18F]fluorodeoxyglucose positron emission tomography/computed tomography; TCZ=tocilizumab.

5 General discussion

In recent years, research in the field of GCA and PMR has increased, and large vessel vasculitis has been recognized as part of the disease spectrum. Imaging plays an invaluable role in the diagnosis of large vessel vasculitis, allowing the detection of subclinical GCA in patients with PMR or the diagnosis of large vessel involvement in patients with non-specific symptoms such as fever or inflammation of unknown origin (20,125,126). However, while imaging is now an integral part of the diagnostic work-up of patients with suspected GCA, routine vascular screening has not yet been implemented in patients presenting with PMR (20). Furthermore, the role of imaging in the follow-up of patients with large vessel vasculitis is less well studied (127).

During my PhD, we were able to demonstrate a high prevalence of subclinical GCA in patients with newly diagnosed PMR who did not have clinical features of GCA and were systematically screened using imaging. We have shown that undiagnosed subclinical GCA in patients with PMR may have severe clinical consequences resulting in more advanced vascular damage when GCA eventually becomes clinically apparent. Furthermore, we have found that unrecognized symptoms of GCA and a long consultation delay contributed to the high incidence of permanent vision loss. Finally, we found that vessel wall oedema on MRI corresponded to pathological FDG uptake on PET/CT, while contrast agent enhancement appeared to be redundant and was seen less frequently than oedema in patients with newly diagnosed LV-GCA. However, vasculitic findings on follow-up MRI and/or PET/CT were not able to predict relapse after treatment discontinuation in patients with LV-GCA.

5.1 Impact of subclinical giant cell arteritis on disease course and outcomes in patients with polymyalgia rheumatica

In our systematic literature review we found that around a quarter of patients with newly diagnosed PMR had subclinical GCA when screened with imaging (49). This finding has been confirmed by the results of recently published cohort studies (50–53). However, PMR is still considered a single disease entity, and clear, validated recommendations to systematically exclude other conditions associated with polymyalgic symptoms are lacking. The high prevalence of subclinical GCA in patients with newly diagnosed PMR suggests that a proportion of individuals diagnosed with GCA and a history of PMR already previously had subclinical GCA. The first study of this PhD thesis thus investigated whether a history of PMR in newly diagnosed GCA is associated with increased vascular damage and ischemic events. The key finding of this retrospective study was that patients with newly diagnosed GCA with a history of PMR had more often ultrasonographic large vessel involvement and vasculitic stenosis at GCA diagnosis compared to patients without prior PMR. However, there was no difference in the rate of ischemic events such as stroke or vision loss between the two groups. Due to the study design, we were not able to show if subclinical GCA was already present at the time of PMR diagnosis, or if vasculitis developed later during the disease course, but the higher rate of vascular stenosis in patients with prior PMR suggests a longer underlying disease process. This supports the hypothesis that patients with a history of PMR may have already had subclinical GCA, with glucocorticoid doses too low to adequately control subclinical inflammation.

Of note, vertebral artery stenosis was significantly more often found in patients with a prior history of PMR in our study, which have been found to be associated with the occurrence of stroke (15). Although we found no statistically significant difference in the rate of ischemic events between the two groups, the number of patients with a stroke (10 events (3.8%) in

patients without prior PMR versus 4 events (8.2%) in patients with prior PMR) might have been too small to find statistically significant differences.

De Miguel et al. recently presented their preliminary follow-up data from their multicenter study comparing the short-term outcome of patients with subclinical GCA to patients with isolated PMR (128). In their study, patients with subclinical GCA were treated with significantly higher initial glucocorticoid doses compared to patients with isolated PMR, but the dose was tapered more rapidly than recommended for GCA. Over a median follow-up period of 21 months, patients with subclinical GCA experienced significantly more often relapses (57.4%) compared to isolated PMR (11.6%), including two major relapses in the subclinical GCA group (128). These findings reinforce the hypothesis that patients with subclinical GCA may need higher glucocorticoid doses than patients with isolated PMR.

On the contrary, the study by Blockmans et al. from 2007 found no difference in relapse rate between patients with and without subclinical GCA. However, in this study, glucocorticoids were rapidly tapered and withdrawn after 6 months in all patients, which is faster than recommended by the later published EULAR/ACR recommendations for the management of PMR (22). This resulted in a high relapse rate of 54%, with most patients relapsing around 6 months after the start of therapy. This may have contributed to an increased number of relapses in patients with isolated PMR, potentially explaining the lack of significant differences compared to patients with subclinical GCA.

The findings of our study have important implications for clinical practice, as they underscore the relevance of subclinical GCA in patients with PMR and add to the evidence that treatment for PMR may be insufficient to fully control subclinical GCA. Our results highlight the necessity of early detection of subclinical GCA and support the implementation of screening strategies for underlying vasculitis in patients with PMR. Furthermore, the importance of educating patients with PMR about the potential progression to GCA needs to be emphasized.

5.2 Permanent vision loss in giant cell arteritis

The second study of this PhD thesis was a retrospective analysis of our large local cohort of patients with suspected GCA, which addressed the incidence and risk factors of permanent vision loss in GCA. The first key finding of the study was that the incidence of permanent vision loss in patients with GCA treated at our center has not decreased over the last 15 years, despite the formal implementation of a fast-track clinic, and remained high at 17.4%. A possible explanation for this finding may be that already before the establishment of a fast-track clinic, it was common practice among primary care providers to immediately initiate glucocorticoid treatment upon suspicion of GCA even before referral for specialist evaluation. This was reflected in our results, where treatment was started a median of two days after first medical contact in patients without visual symptoms and on the same day in those patients with visual impairment. Thus, the implementation of a formal fast-track clinic may not have further reduced the delay from first consultation to treatment initiation in our institution.

While fast-track clinics expedite referrals from primary care and facilitate rapid access to specialist evaluation, they remain unable to reduce the time between symptom onset and initial evaluation for suspected GCA (67). In keeping with this, the second key finding of this study was that the time from GCA-symptom onset to seeking first medical attention contributed most to the diagnostic delay. Notably, this delay was significantly longer in patients who experienced vision loss compared to those who did not. Furthermore, most patients who suffered from vision loss only sought medical attention after the onset of visual impairment, although more than half of these patients had experienced GCA-related symptoms a median of 3 weeks before the onset of vision loss. In five patients, diagnosis of GCA was missed at the initial evaluation, leading to a delay from first consultation to specialist referral.

As third key message, we found that older age and jaw claudication were significantly associated with permanent vision loss, corroborating the results of previous studies (71,129–

131). Finally, expanding on findings from earlier investigations, we found that the number of temporal artery vessel segments showing vasculitis on ultrasound was significantly higher in patients who experienced permanent vision loss compared to patients who did not. However, 7.4% of patients without vasculitic ultrasonographic findings in the temporal artery still experienced vision loss, stressing the fact that glucocorticoid initiation should not be delayed in case of suspected GCA, irrespective of ultrasound findings.

Taken together, this study provided a detailed assessment of the various stages in the patient's pathway that led to a delay in diagnosis. Our findings indicate the need for more extensive disease awareness programs, both among the public and primary care providers.

5.3 Comparison of MRI with PET/CT and ultrasound in the assessment of large vessel giant cell arteritis

The most appropriate imaging modality for the diagnosis of LV-GCA depends on the local setting and available expertise, and involves weighing the advantages and disadvantages of each imaging modality (20). Factors to consider in choosing the best method involve the availability, cost, radiation exposure, and pretest probability of differential diagnoses (20,84). Advantages of ultrasound include its good availability and absence of radiation; however, it is operator dependent and does not allow the assessment of the thoracic aorta. PET/CT offers a broad detection of metabolic activity and differential diagnoses at the expense of radiation and high cost. MRI allows the combined assessment of morphological and inflammatory changes and does not expose the patient to radiation (20,84). However, standardized criteria for the interpretation of large vessel vasculitis on MRI are lacking (20).

In our third study, we therefore compared MRI findings to PET/CT and/or ultrasound on a segmental level to identify parameters on MRI which correspond to large vessel vasculitis. The first main finding of this study was that vessel wall oedema on diffusion-weighted sequences

on MRI corresponded to vasculitic PET/CT findings while non-oedematous mural thickening was found in two segments only on MRI, one of which did not show any FDG uptake on PET/CT. In the axillary segment, contrast agent enhancement was less frequently found compared to oedema and did not increase the yield of pathological findings on MRI in our study.

The second key finding was that pathological vessel segments on MRI had a low agreement with vasculitic ultrasound findings. This implies that the way vasculitis appears on ultrasound is different from vasculitic features seen on MRI. Imfeld et al. showed that findings on PET/CT and ultrasound were often discrepant in the same vessel segment and should be considered complementary rather than congruent imaging modalities (132). Similarly, our study suggests that MRI and PET/CT on the one hand, and ultrasound on the other hand visualize different features of vasculitis. This finding supports the use of a second imaging modality in cases of suspected GCA but ambiguous clinical, laboratory or histological findings (132). However, glucocorticoid treatment prior to imaging may have affected the sensitivity of MRI and ultrasound differently, possibly explaining the discrepant results in our study.

5.4 The value of imaging to predict relapses after treatment discontinuation in large vessel giant cell arteritis

While imaging is well established in the diagnosis, its role in the follow-up of patients with LV-GCA is unclear (20,127,133). We therefore evaluated the utility of PET/CT and MRI performed at the time of treatment discontinuation in predicting subsequent relapses. The key finding of this study was that none of the qualitative or quantitative imaging parameters was able to reliably predict relapse within 4 months after treatment stop in patients with LV-GCA.

Previous reports investigating the ability of imaging to predict relapse performed imaging during different stages of the disease course, included heterogenous patient populations and

relapses were recorded during ongoing treatment (77,108,109). The novelty of our study was that we performed PET/CT and MRI systematically at the end of treatment in patients with LV-GCA. Furthermore, we assessed a wide variety of quantitative and qualitative imaging parameters for their ability to predict subsequent relapses.

We defined vasculitis on PET/CT as SUV_{max} artery-to-liver ratio >1 for the supra-aortic vessels and >1.3 for the aorta and femoral region (82,91). Based on the findings from our third manuscript, we defined vasculitis on MRI as the presence of oedematous vessel wall thickening with or without contrast agent enhancement. None of the examined parameters on MRI was statistically significantly different between patients who relapsed and those who remained in remission, corroborating a smaller study which performed MRA systematically at treatment stop in patients with GCA (36). On PET/CT, we found a slight tendency to a higher number of positive PET/CT segments and a higher sum of all SUV_{max} artery/liver ratios in relapsing patients, however, this did not reach statistical significance. This may lead to the hypothesis that parameters assessing the overall severity of vascular involvement on PET/CT may have some predictive value compared to the sole binary assessment of the presence or absence of vasculitis on imaging. However, larger studies are needed to confirm this hypothesis.

The significance of signs of active vasculitis on imaging in patients who are planned to stop treatment remains unclear. Previous studies have shown an association between an increased FDG uptake at diagnosis of patients with GCA and the development of aortic complications during follow up (134,135). However, prospective long-term follow-up studies assessing the significance of vasculitic imaging findings at treatment discontinuation for the development of aneurysms or dissections are lacking.

Taken together, our findings do not support the use of imaging performed at treatment stop to assess the risk for subsequent relapse and highlight the need for continued research into

effective predictive biomarkers. The role of imaging in predicting the development of aortic complications remains to be elucidated.

5.5 Strengths and limitations

The first and second manuscripts presented in this PhD thesis are based on our local cohort of patients with suspected GCA. The major strengths of the cohort are the large sample size, the numerous variables collected, and the extensive documentation of ultrasound findings. Each arterial segment was re-assessed and categorized by an experienced angiologist, resulting in more than 10,000 documented vessel segments, adding major value to the cohort. This extensive cohort allowed us to stratify the patients according to their vascular involvement, to conduct subgroup analyses and to calculate summary scores of the affected arteries.

The main limitation of this cohort is its retrospective design, which may have compromised the reliability and accuracy of the data, due to the lack of a standardized collection of clinical and laboratory variables (136). Although we attempted to adjust for potential confounders using statistical methods, we were not able to prove causality due to potential residual confounding and persisting bias which may lead to false associations (136).

Strengths of our third study include the detailed analysis and comparison of imaging findings on a segmental level. Furthermore, this was the first study which provided head-to-head comparisons of three different imaging modalities in the diagnosis of LV-GCA. However, the study was limited by its small sample size. Imaging was not performed at the same day and different durations of glucocorticoid treatment might have differently impacted the results of the imaging modalities. In addition, the study design did not allow us to calculate the diagnostic performance of MRI in the diagnosis of LV-GCA.

Strengths of our fourth study investigating the role of imaging to predict relapses after treatment discontinuation include the prospective design and the systematic performance of imaging

during clinical remission, when treatment withdrawal was planned or had already occurred. Limitations include the heterogenous assessment of the patients using either MRI or PET/CT or both. Since our study was exploratory in design, the sample size may have been too small to find significant differences between patients who relapsed and those who remained relapse-free.

6 Conclusion and outlook

This PhD thesis sheds light on specific research gaps in the field of GCA and PMR. Based on our findings, the following implications for clinical practice and the management of individuals with GCA or PMR can be drawn:

1) **Screening for subclinical GCA.** Subclinical GCA in PMR may lead to more advanced vascular damage. Coupled with the high prevalence and the lack of consistent and reliable clinical or laboratory predictors of subclinical GCA our findings highlight the need for early screening strategies and tailored treatment of subclinical GCA in patients with PMR.

2) **Raising public and physician awareness of GCA manifestations.** The incidence of permanent vision loss in our institution remains high. The time from symptom onset to first consultation mainly contributed to a delay in diagnosis. This underscores the need to raise public awareness about the severe consequences of GCA and the importance of timely medical treatment. Educating both patients and physicians about early symptoms and signs of GCA is essential to further reduce the diagnostic delay.

3) **Oedematous wall thickening on MRI corresponds to large vessel vasculitis on PET/CT.** We found that wall thickening in combination with mural oedema most often corresponded to large vessel vasculitis on PET/CT. Mural contrast enhancement did not increase the yield of pathological findings. MRI and ultrasound seem to provide complementary rather than congruent findings.

4) **Limited utility of imaging to predict relapse after treatment stop in LV-GCA.** Neither qualitative nor quantitative parameters on PET/CT or MRI performed at the end of treatment predicted subsequent relapses in patients with LV-GCA. Overall, our results do not support the use of imaging to identify patients at increased risk of relapse after

treatment stop. The significance of persistent imaging findings for long-term complications such as aortic aneurysms and dissections remains to be clarified.

In conclusion, the results of this PhD thesis highlight the importance of early detection and appropriate treatment of GCA to prevent vascular and ischemic damage. While imaging plays a central role in the diagnosis of GCA and in screening for subclinical GCA, its ability to predict relapses after treatment discontinuation seems limited.

6.1 Directions for future research

Building upon the insights of this thesis into the field of large vessel vasculitis in GCA and PMR, this section provides an outlook on further studies that are currently underway and suggests directions for future research.

The high prevalence of subclinical GCA in PMR and the accumulating evidence of its impact on the outcome of PMR reinforces the need to investigate appropriate treatment strategies for patients with subclinical GCA in PMR. Future studies are needed which stratify GCA and PMR patients based on their clinical and imaging characteristics and explore the influence of different GCA and PMR phenotypes on disease progression and outcome. This could allow physicians to develop tailored and effective treatments strategies according to disease phenotype (137,138).

Furthermore, to enhance accurate diagnosis of PMR and potential subclinical GCA, the implementation of fast-track clinics for suspected PMR should be addressed (54,139,140) and future research efforts are needed to investigate the benefits of early referral strategies of suspected PMR compared to usual care (119). Forthcoming recommendations from the 'International PMR Referrals Recommendation Group', in which I had the opportunity to participate, will elaborate on the early referral of patients with suspected PMR (manuscript in preparation).

To further explore potential explanations for interindividual differences in glucocorticoid responses in patients with PMR and GCA, we aim to investigate individual differences in glucocorticoid metabolism in relation to response to glucocorticoid treatment in a prospective cohort study of patients with new-onset PMR and/or GCA (ClinicalTrials.gov identifier: NCT05479448). Results of this study will help to identify individuals with glucocorticoid resistance, allowing for a more intensive treatment approach and rapid implementation of glucocorticoid sparing agents. Furthermore, by comprehensively understanding the interplay between individual glucocorticoid metabolism and patient response to glucocorticoid treatment, profiles of steroid responders may be delineated. These profiles may be prospectively assessed in future randomized controlled trials.

Lastly, the relevance of pathological findings on imaging performed at treatment stop in patients with LV-GCA in clinical remission remains unknown. Prospective cohort studies examining the long-term progression of disease and development of aortic aneurysms and dissection may help to elucidate the relevance of pathological imaging findings and further aid to guide treatment decisions.

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    - Reformulation of text passages