

Giant cell arteritis-a report on systematic physical evaluation and large vessel involvement as a prognostic risk factor for complicated disease course, real life data.

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Abstract

Background: Large vessel involvement (LVI) as a prognostic factor regarding flare frequency and glucocorticoid (GC) demand has not been investigated in giant cell arteritis (GCA). LVI may indicate a complicated disease course but periodic imaging is not an accepted norm for reevaluation and data on findings of vascular damage with clinical vascular assessment is scarce.

Objectives: This study was conducted to explore periodic peripheral vascular evaluation as a tool for a) detecting smouldering disease, b) identifying LVI, and c) to investigate whether LVI predicts frequent flares on high dose GC.

Methods: A portion of all consecutive newly diagnosed patients with GCA and polymyalgia rheumatica, referrals for second opinion or initiation of GC-sparing drug in patients with these diagnoses between July 2011 and May 2015 were evaluated and followed on regular intervals by one rheumatologist. Only those with GCA were included. Patients were evaluated at follow-ups with auscultation of the heart and peripheral vessels, palpation of the peripheral pulses and pressure measurement of the brachial and dorsal pedal arteries. Imaging was done if: new vascular bruit or pressure asymmetry, frequent flares, long standing disease or rise in inflammatory markers without any other explanation.

Results: Imaging revealed LVI in 58% (LV-GCA). Sixty-five percent developed pressure asymmetry, 65% of them had LVI. With pressure measurements 73% of those with LV-GCA could be found. Six patients exhibited a relapsing and remitting course of pressure asymmetries. Thirty-one percent of the ankle pressure asymmetries (APA) at baseline were due to vasculitis. APA occurred significantly higher in LV-GCA patients ($p=0.0017$). Sixty-five percent of the patients had flares on high dose GC, 76% of them had LVI ($p=0.014$).

Conclusions: Periodic vascular assessment is reliable to I) use as an independent activity marker, II) evaluate treatment efficacy, III) detect LVI and smouldering inflammation. LVI predicts a complicated disease course.

Keywords: Giant cell arteritis, Imaging, Temporal artery biopsy, Brachial pressure measurement, Ankle pressure measurement.

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Introduction

Giant cell arteritis (GCA) is the most common primary systemic vasculitis. Its generalized nature was early recognized [1] but over time forgotten with more focus being on the classical cranial GCA (C-GCA). The concept of its widespread nature has been re-established in recent years through modern imaging technology i.e. computed tomography with angiogram (CTA), positron emission tomography with computed tomography (PET-CT), magnetic resonance angiography (MRA) and colour Doppler sonography (CDS) [2-5].

Large vessel involvement (LVI) as a prognostic factor with regard to flare frequency and glucocorticoid (GC) demand in GCA patients (LV-GCA) has not been investigated in depth, although there are some publications suggesting a more complicated disease course when LVI is present [6-10] but also others that don't show any difference [3,11].

Today the disease activity is primarily assessed by the presence of ischemic symptoms from the cranial region, polymyalgia

rheumatica (PMR) symptoms, systemic symptoms (i.e. fever, chills, weight loss, fatigue) and the levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) but not by regular evaluation of the peripheral vessels.

So far there are no specific diagnostic or activity biomarkers. An elevated ESR is viewed as mandatory for the diagnosis and is used to monitor disease activity during follow-ups. Unfortunately neither ESR nor CRP separately or combined are infallible. At the time of diagnosis 22.5- 44% of the patients have normal ESR [12-14] and 0.8-4.0% have both normal ESR and CRP [15-18]. During follow-up about 15-48% of the flares occur without raise in ESR [13,19-21]. Thus there is an unmet need in the assessment of disease activity, and the need is even greater now when biologic treatment is part of the treatment arsenal, the foremost being tocilizumab. Tocilizumab is an IL-6 inhibitor that as part of its mechanism of action extinguishes the inflammatory response.

Today there is no standardized method to regularly assess the vascular damage. Periodic imaging is not an accepted norm for

follow-up in GCA, but is uncontroversial in Takayasu's disease, another large vessel vasculitis. Periodic imaging with CTA, the most accessible imaging modality, is not advisable with regard to repeated exposure to radiation. MRA is not readily available and is more costly.

There are very few data on the prevalence and findings of vascular damage with clinical peripheral vascular assessment in GCA patients [22,23].

The aims of this study are i) to explore the potential usefulness of periodic peripheral vessel evaluation as a tool for a) detecting smouldering disease, b) identifying large vessel involvement (LVI), and ii) to investigate whether the presence of LVI predicts a complicated disease course with frequent flares on high dose GC.

Methodology

Patient selection

The hospital of Kristianstad is a county hospital, serving a population of 170,000 in a region with both rural and urban areas. The rheumatology clinic comprises four rheumatologists, working part-time in varying degrees.

Patients with GCA and PMR with newly-onset disease, referrals for second opinion evaluation or the initiation of GC-sparing drug (GCSD) are evenly distributed among the physicians. All consecutive patients, between July 2011 and May 2015, to one of the rheumatologists were followed regularly according to a specific regime in a pilot project. Only patients with GCA with at least two visits beyond the baseline evaluation were included in this study.

Aims

The project setup was adapted to everyday clinical practice and was conducted for several reasons, among others, to: 1. test the value of the often taught but rarely applied teaching of bilateral brachial pressure measurement in conjunction with this disease, 2. test the potential merit of adding ankle pressure measurement to the clinical evaluation, 3. evaluate if eventual fluctuations in pressure measurements could serve as a reliable disease activity indicator, 4. confirm or refute the suspicion that patients with LVI suffer from a more complicated disease course, and 5. form an own opinion on the efficacy of methotrexate (MTX), leflunomide (LEF) and mycophenolate mofetil (MMF) as GCSDs.

Initial evaluation

All patients were questioned and physically evaluated at the baseline visit according to a defined protocol. They were for instance inquired about specific symptoms related to a compromised cranial and/or distal circulation and baseline measurements of brachial and ankle pressures were obtained. The levels of ESR, CRP, platelets (Plt) and haemoglobin (Hb) before GC initiation were recorded.

Follow-ups

Regular visits every four months the first year, every six months the second and third year and then annually. Extra visits were scheduled as needed. ESR, CRP, Plt and Hb values were

obtained within a week of each visit and prior to every GC dose reduction.

The heart was auscultated, peripheral vessels were auscultated and palpated and the brachial and ankle pressures measured. The presence of heart murmur, vessel bruit, asymmetry of brachial and/or ankle pressure ≥ 10 mmHg at the first visit or at follow-ups was noted as significant and recorded. Inquiries were made about symptoms related to compromised circulation in addition to new or return of previous disease related symptoms/signs. The patients were followed until death, remission, change of care unit, change of diagnose or the end of the project 2016-04-11.

Vascular assessment

The patient in a supine position, the head end of the bed raised 30 degrees. The superficial common temporal, facial, occipital, common carotid, subclavian, axillary, brachial, common femoral and renal arteries were auscultated and the radial and common femoral pulses were palpated.

Brachial pressure measurement with a cuff attached to each arm, inflated simultaneously with automatic sphygmomanometers (Boso Medicus), after 5 minutes rest.

Ankle pressure measurement with a 8MHz Doppler pen probe (Huntleigh Dopplex D900) and a cuff size of 12 cm, with the cuff position just proximal to the malleoli. The systolic pressure at which the Doppler sounds were first audible while deflating the cuff, were recorded. Only the dorsal pedal arteries were measured, if this was not possible posterior tibial arteries were then measured.

Glucocorticoid regimen

Initial dose, prednisolone 60 mg/day if with and 40 mg/day if without eye manifestations at presentation regardless of weight, continued until normalization of inflammatory markers, then reduction by 5 mg/week to 20 mg, then by 2.5 mg/week to 10 mg, then by 1.25 mg/6-8 weeks.

When flares occurred, the GC dose was raised to the previous dose that kept the inflammation in check.

GCSD Regimen

The first-line GCSD, MTX was changed over time due to the treatment results of the first eight (two not included in this study) patients and following published case-series with other GCSDs.

Imaging

PET-CT and CTA were employed or previous imaging with contrast enhanced CT thorax with or without abdomen were reviewed (if available), if: new vascular bruit, new or progress of baseline pressure asymmetry, high flare frequency (defined as ≥ 3 flares) on high dose of GC (defined as a prednisolone dose ≥ 15 mg/d) or at low dose, long standing disease or if none of the above but rising inflammatory markers without any other explanation. Over time, all patients were scanned.

Repetitive imaging evaluations were not part of the protocol and were only performed in a few exceptional cases after confirmation of LVI. With the focus being on whether LVI was present or not, data collection was not designed to account

for the different types of imaging findings reflecting vasculitis. Only aneurysms were recorded separately.

The study was approved by the Regional Research Ethics Committee for Southern Sweden, reference number 2016/165.

Statistical analysis

Chi-square/Fisher's exact test was used to compare categorical data and Student's *t*/Mann-Whitney *U* test to compare continuous data as appropriate. The statistical analysis program SPSS 23 was used.

Results

The GCA cohort

Forty patients were identified, 26 (23 biopsy-proven) fulfilled the inclusion criteria, the rest were excluded due to loss to follow-up, death shortly after inclusion, follow-up not following the protocol, move to another care unit or to nursing homes and non-compliance. Twenty-three patients were newly diagnosed, two started as longstanding PMR in need of GCSD and one as referral for second opinion PMR; these three were diagnosed with GCA during follow-up.

GCA phenotypes: So called PMR (SC-PMR), clinically pure PMR but with vasculitic findings *n*=2, GCA with PMR *n*= 11, GCA *n*=10, Occult-GCA, patients with no classical signs or symptoms of GCA, with fever of unknown origin (FUO) or inflammation of unknown *n*=3.

Fifteen (58%) were females. The mean age at disease-onset 71.5 years (41.1-81.6) and the mean disease duration 5.5 years (1.1-29.6). Five patients had a pre-existing diagnosis of

PMR with ongoing GC treatment 2.4, 2.4, 3.4, 21.9 and 27.2 years respectively before the GCA diagnose, three developed cranial symptoms and one never did have any. Transient visual symptoms occurred in 7 (27%) and permanent visual impairment in 2 (8%) of the patients (Table 1). Two deaths occurred during follow-up, caused by acute myocardial infarction and pulmonary embolism.

Laboratory findings

There was no significant difference between the two groups regarding the inflammatory markers (Table 1). A high prevalence of HLA-DRB1*04:16/23 (70%) was observed in the cohort but no significant difference between GCA patients with or without LVI nor between those with flares on high dose GC or those without.

Imaging results

PET-CT *n*=21, CTA *n*=4, PET-CT & CTA *n*=9 (one just CTA of the epiaortic vessels) and review of available CT-thorax-abdomen with contrast only *n*=1 patient.

One patient with PET-CT had indeterminable hypermetabolism in the mediastinal pool (included in the C-GCA group for further analysis).

In the nine cases with CTA and PET-CT both results conformed in four cases: no vasculitis *n*=3, vasculitis and the same extent *n*=1, in five the results diverged: CTA negative but PET positive *n*=1, CTA positive but PET negative (ongoing prednisolone 17.5 mg/day) *n*=1, CTA and PET both positive but different extent, PET with more extensive vasculitis *n*=3.

Table 1. Demographic data and baseline clinical characteristics.

| | LV-GCA (n=15) | C-GCA(n=11) |
|---------------------------------------|------------------|------------------|
| Female sex, n (%) | 8 (53%) | 7 (64%) |
| Age (yrs), median [range] | 70.0 (41.1-81.6) | 74.8 (62.4-81.5) |
| Disease duration (yrs), median (IQR) | 2.6 (1.5-8.3) | 3.9 (3.5-4.9) |
| Diagnostic delay (mths), median (IQR) | 2.2 (1.0-10.4) | 1.9 (0.5-2.9) |
| Positive TAB, n (%) | ● 14 (93%) | 9 (82%) |
| HLA-DRB1*04, n (%) | 8 (67%) | 8 (73%) |
| ESR (mm/h), mean (SD) | 76 (26) | 67 (26) |
| CRP (mg/L), median (IQR) | 67 (50-156) | 86 (48-150) |
| Plt (x10 ⁹), mean (SD) | 384 (89) | 367 (62) |
| Hb (g/L), mean (SD) | 112 (12) | 118 (11) |
| Thrombocytosis | 8 (62%) | 6 (55%) |
| PMR | ■ 8 (53%) | 5 (46%) |
| Transient visual symptoms | 5 | 2 |
| Permanent visual impairment | 2 | 0 |
| Never smokers | 7 | 5 |
| Ever smokers | 8 | 6 |
| Hypertension | 6 | 7 |
| Phenotypes represented, n | | |
| GCA+ PMR | 4 | 6 |
| GCA | 7 | 3 |
| SC-PMR | 2 | 1 |
| Occult-GCA | 2 | ◆ 1 |
| High dose GC-demand, n (%) | ♣ 13 (87%) | 4 (36%) |

Yrs, years; IQR, interquartile range; mths, months; TAB, temporal artery biopsy; ●, two patients with bilateral biopsies; ■, including atypical ones: cervical only *n*=2 and upper extremity only *n*=1; Thrombocytosis, Plt >348 x 10⁹/L for men and >387 x 10⁹/L for women; Ever smokers, present and past smokers; ◆, clinical presentation as occult with fever and chills, PET-CT finding in the mediastinal pool indeterminable; ♣, *p*=0.014; Missing data: Plt LV-GCA *n*=2; ESR LV-GCA *n*=1; Hb LV-GCA *n*=1; HLA-DRB1*04 LV-GCA *n*=3.

Arteries involved: Vertebral n=5, common carotid artery (CCA) n=7, innominate n=6, subclavian n=8, axillary n=5, brachial n=3, aortic arch n=5, ascending aorta n=3, descending aorta n=7, abdominal aorta (AA) n=7, coeliac trunk n=4, superior mesenteric (SMA) n=4, renal n=3, common iliac (CIA) n=6, external iliac n=5, common femoral artery (CFA) n=5, superficial femoral (SFA) n=8, deep femoral (DFA) n=3, popliteal n=2, crural n=3. Aneurysms, one each: AA, SMA and coeliac trunk.

Physical findings

One patient had only brachial pressure measurements due to rigid lower extremity vessels.

Newly developed physical findings: heart murmur n=8, vessel bruit n=5, pressure asymmetry brachial n=10 and ankle n=15 (Tables 2 and 3). 17/26 (65%) patients developed pressure asymmetries during follow-up, 11/17 (65%) were caused by vasculitis. Thirteen patients had baseline ankle pressure asymmetries, seven progressed, four of which were caused by vasculitis. Two LV-GCA patients had only ankle pressure asymmetries throughout follow-up and two others had initially only ankle pressure differences. One patient developed progressive systemic hypertension caused by bilateral renal artery vasculitis.

Distribution of pressure asymmetries: upper extremity (UE) n=1, lower extremity (LE) n=2, UE+LE n=8. Six patients developed several findings concomitantly, one example: brachial + ankle

Table 2. Distribution of the physical findings among the LV-GCA and C-GCA patients.

| | At initial visit | | At follow-up | |
|-------------------------------------|------------------|-------|--------------|-------|
| | LV-GCA | C-GCA | LV-GCA | C-GCA |
| Heart murmur | 2 | 3 | 3 | 5 |
| Vessel bruit | 3 | 0 | ♣4 | 1 |
| Brachial pressure difference, Total | 1 | 0 | 8 | 2 |
| Progress # | | | 2 | 0 |
| New | | | 6 | 2 |
| Ankle pressure difference, Total | 8 | 5 | *12 | 3 |
| Progress | | | 7 | 0 |
| New | | | 5 | 3 |

♣, vessel bruit location: common carotid n=2 bilaterally, left axillary artery n=1, right axillary artery n=1, subclavian artery n=1 (heard above and below the clavicle), common femoral artery n=1 bilaterally; #, at first visit <10 mmHg; *P=0.0017.

Table 3. Time (months) from diagnose to occurrence of physical findings in the LV-GCA group.

| | |
|---|----------------------|
| Brachial asymmetry, median (SD) [range] | 8.1 (6) [1.7-22.1] |
| Ankle asymmetry, median (SD) [range] | 8.7 (10) [1.7-35.9] |
| Vessel bruit, median (SD) [range] | 17.4 (11) [3.1-32.9] |
| Heart murmur, median (SD) [range] | 13.0 (11) [0.6-26.3] |

pressure asymmetries + vessel bruit + heart murmur.

15/26 (58%) had LV-GCA and 11/15 (73%) of them could be found with pressure measurements.

Wax and waning of pressure asymmetries

Six patients exhibited a relapsing and remitting course of pressure asymmetries. A compilation of the values at baseline and at first occurrence for all patients is presented (Table 4). Two examples:

A 78 year old male with disease-onset in the beginning of May 2013 and the sole clinical symptom of new headache at the top of his head, was diagnosed with GCA one month later. Temporal artery biopsy (TAB) was positive. Due to frequent flares on high dose of prednisolone (about 25-30 mg/d) a CTA was done in the middle of June 2013 with no vasculitis. In the end of April 2014 new brachial and ankle pressure asymmetries were noted, prednisolone 3.75 mg/day; ESR 22, CRP 7.8. PET-CT in the end of May showed widespread vasculitis in the following arteries: CCA, innominate, subclavian, axillary, brachial, entire aorta, coeliac trunc, SMA, CIA, external iliac, SFA and DFA. Prednisolone was increased to 15 mg/d and LEF initiated 10 mg/day in the end of June. At visit in the middle of August complete remission of the pressure asymmetries (even the baseline ankle pressure difference of 20 mmHg), prednisolone 15 mg/day, LEF 10 mg/day; ESR 15, CRP 3.8. Prednisolone was tapered and LEF was escalated to 15 mg/day. Very slowly raising CRP and Plt was noted from October 2014 to the end of January 2015, LEF was escalated to 15 mg 3 days/week and 20 mg 4 days/week. At visit in the beginning of February 2015 a recurrence of ankle pressure asymmetry was noted, prednisolone 5 mg/day, LEF 15 mg/day 3 days/week and 20 mg 4 days/week; ESR 4, CRP 6.4. Medication left unchanged due to recent LEF escalation. Follow-up in the beginning of May with normalized ankle pressure, prednisolone 5 mg/day, LEF 15 mg 3 days/week and 20 mg 4 days/week; ESR 8, CRP 2.9. Prednisolone was reduced to 3.75 mg/day and LEF increased to 20 mg/day. At follow-up in the end of September situation unchanged but at the last visit in the beginning of March 2016 recurrence of the ankle pressure asymmetry and new vessel bruits over both CFAs were noted, prednisolone 3.75 mg/day, LEF 20 mg/day; ESR 16, CRP 4.4. MTX addition was planned but the patient declined. Prednisolone was escalated.

A 72.1 year old female with FUO since the beginning of September 2013 was diagnosed with occult-GCA at the end of the month when CT-thorax-abdomen showed vasculitis of the infrarenal AA and the proximal CIAs. PET-CT five weeks later revealed widespread vasculitis affecting bilateral vertebral, subclavian and axillary arteries, the entire AA and the left CIA. TAB was negative. Due to frequent flares at high doses of prednisolone (>50 mg/day initially, later 35 mg/day) MMF was initiated in the beginning of October 2014, escalating to 3 g/day. At follow-up in the middle of April 2015 a new heart murmur + vessel bruit + brachial pressure + progress of baseline ankle pressure asymmetry was noted, prednisolone 10 mg/day, MMF 3 g/day; ESR 10, CRP 6. CTA showed progress of the vasculitis in the subclavian and axillary but regress in the AA and the iliac arteries. MMF was discontinued. Subcutaneous MTX was added in the beginning of May, rapidly escalating to 30 mg/week. At follow-up in the end of November complete remission of brachial pressure asymmetry, disappearance of vessel bruit and return of ankle pressure asymmetry to baseline value was observed, prednisolone 8.75 mg/day, MTX 30 mg/week; ESR 3.0, CRP 3.7. GC was tapered. At the last follow-up in the beginning of

Table 4. Clinical data at baseline and at the first occurrence of pressure asymmetry.

| GC Init. dose | Baseline | | | | At the first pressure difference/progress | | | |
|---------------|---------------|----------|---------|---------|---|----------|---------|---------|
| | GC flare dose | ESR, CRP | BP R/L | AP R/L | GC | ESR, CRP | BP R/L | AP R/L |
| 40 | 40 | 61, 54 | 175/175 | 170/165 | 40 | 18, 11 | 178/177 | 170/180 |
| 60 | 45 | 55, 58 | 149/142 | 185/180 | 17.5 | 18, 1.9 | 140/160 | 140/200 |
| 30▼ | 25-30 | 70, 51 | 132/127 | 140/160 | 3.75 | 22, 7.8 | 141/124 | 140/180 |
| 50 | 35-40 | 53, 75 | 144/138 | 160/150 | 10 | 10, 6.0 | 164/152 | 200/150 |
| 60 | 10-20 | 18, 1.2 | 156/156 | 180/160 | 10 | 13, 2.0 | 187/176 | 220/200 |
| 60 | 25 | 49, 47 | 164/157 | 160/180 | 40+ CYC ♪ | 2, 0.7 | 124/136 | 70/150 |
| 70 | 25-35 | 134, 211 | 160/159 | 160/158 | 30 | 12, 0.9 | 145/158 | 125/115 |
| 65 | 50-55 | 90, 158 | 136/136 | 125/125 | 12.5 | 2, 1.6 | 140/148 | 150/130 |
| 30● | 17.5 | 91, 155 | 210/181 | 200/205 | 20 | 19, 7.5 | 139/133 | 150/130 |
| 30♦ | 15 | 104, 64 | 194/190 | 65/110 | 30+ CYC ♪♪ | 9, 2.5 | 170/180 | 60/150 |
| 15■ | 15 | 50, 23 | 130/136 | 200/170 | 25+ MTX | 14, 2.1 | 130/155 | — |

GC flare dose, the prednisolone dose at which flares occurred; BP, brachial pressure (systolic); AP, ankle pressure; ▼, GC treatment initiated by general practitioner; CYC, cyclophosphamide; ♪, at the third cyclophosphamide pulse; ●, Under investigation for FUO at the clinic of infectious diseases, with suspected but unconfirmed GCA; ♦, Second opinion PMR; ♪♪, at the sixth cyclophosphamide pulse; ■, Referred due to arthritis, with ongoing GC for previous PMR, GCA diagnosed at first visit; —, missing data.

March 2016 increasing frequency of episodes with chills and low-grade fever was reported and deterioration of the ankle pressure asymmetry was noted, prednisolone 3.75 mg/day, MTX 30 mg/week; ESR 9, CRP 19. GC-dose was escalated but the patient wished to await the switch to LEF.

Distribution of LVI and patients with high flare frequency on high dose GC

Of the ten youngest (41.1-70.0 years old) and of the ten with longest diagnostic delay eight and seven patients respectively were LV-GCA. Within the cohort seventeen patients had frequent flares on high dose GC, thirteen were LV-GCA patients (Table 5).

Table 5. Distribution of patients with high flare frequency on high dose GC.

| The entire cohort 17/26 (65%) | LV-GCA 13/15 (87%) | C-GCA 4/11 (36%) |
|----------------------------------|-----------------------|---------------------|
| Median dose at flares (mg/day) | 28 | 25 |
| Interquartile range (mg/day) | 18-40 | 19-38 |
| Range GC dose at flares (mg/day) | 15-53 | 18-43 |

Discussion

To the best of my knowledge this is the first study to evaluate the role of periodic peripheral vessel assessment (upper and lower extremities) as a tool to detect grumbling disease and large vessel damage, at the time of diagnosis and during follow-ups.

It is also the first study to illuminate the “natural course” of large vessel damage during the early phase of the disease, by its periodic nature. Finally, to the best of my knowledge, there are no other studies specifying flares on high dose GC or compare this aspect between those with and without LVI. This is the second study with prospectively followed patients, to show the impact of LVI as a prognostic factor regarding GC demand.

The presence of LVI in this cohort was 58% which is in keeping with previous prospective studies 45.4-83% [2-4]. With periodic vascular assessment could, 73% of those with LV-GCA be detected. In a study of 32 patients with established GCA (mean disease duration 2.9 years, range (0-13), imaging and physical vascular evaluation (both epiaortic vessels only)

detected at least one lesion in 75% and physical findings in 53% of the patients respectively [23] and in another study with 24 newly diagnosed GCA patients, imaging and physical vascular evaluation at initial visit only (upper and lower extremities), detected lesions in 79% and physical findings in 42% of the patients respectively [22]. Sole assessment with physical evaluation, would miss 27-47% of the patients via LVI. As the results of this study indicate, physical abnormalities accumulate over time which can explain the higher yield in this study and the one with the established GCA cohort.

The number of pressure changes occurring in the LV-GCA group, indicate that the occurrence of pressure asymmetry is the rule rather than the exception and demonstrates that the inflammatory activity is still high even beyond the first year. Atherosclerosis becomes highly improbable when the changes appear within a few months after diagnosis and markedly improve or disappear after treatment, proof of concept. As it has been shown the occurrence of change in the ankle and/or brachial pressure difference, despite normal or low grade rise in inflammatory markers, is a reliable activity indicator.

Also as shown, asymmetric ankle pressure at baseline can be an expression of underlying vasculitis since 31% of the pre-existing pressure differences were caused by it. Vasculitis of the lower extremity is not rare, its reported frequency being 18-53.5% [3,22-25]. To measure brachial but omit the ankle pressure would result in a loss of sensitivity to detect underlying LVI. For example, in a few patients the asymmetric ankle pressure manifested itself before the brachial one and there were also two patients with only ankle pressure asymmetries, in these cases the diagnosis of LVI would be delayed or missed. There was a significant difference in the occurrence of ankle pressure asymmetry between patients with and those without LVI, $p=0.0017$.

The frequency of and time to development of vessel bruit was much lower and longer, compared to that of pressure changes, making it a less useful screening tool. The time to development of stenosis in this study is in keeping with previous reports [26-28].

The pitfalls of physical vascular evaluation are: if only visceral and/or internal arteries are affected no pressure asymmetry can be detected, also if extremity-vessels are affected bilaterally (which is the norm) and equally there will be no apparent pressure difference until one is more diseased or becomes healthier than the other (one patient). The 10 mmHg cut-off value yields high sensitivity and signals a need for further investigation. This threshold has been proven relevant in prior studies [23,29].

The high proportion of GCA patients with flares in this cohort is in keeping with previous studies 53.3-92% [7,30-33]. In the LV-GCA group, a significantly higher proportion of patients had flares on high dose GC and required GCSD (87% vs. 36%, $p=0.014$). The higher flare frequency being in the LV-GCA group is in keeping with two other recent studies [7,9] but this is the first study to specify flares on high dose GC and compare this aspect between GCA patients with and without LVI.

In this cohort the LV-GCA group showed a trend toward younger age at disease-onset and longer diagnostic delay, in keeping with recent studies [7,9,34]. In contrast to these studies, there was not any significantly higher proportion females in the LV-GCA group.

The patient with disease-onset at the age of 41.1 could be argued to have TAK, but in favor of GCA are: a) over the years recurrent periods with classic cranial ischemic symptoms which are much less common in TAK, b) a non-occlusive disease course involving solely the abdominal aorta despite long standing disease, while in TAK vascular damage accumulate over time and is usually occlusive in nature [35,36] and c) a positive TAB.

CTA is the most accessible imaging technique. The illustrated cases point to the possibility that it may not be sensitive enough. This poses a potential risk for misclassification of LV-GCA patients as non-LV-GCA. Similar finding was reported in a recent study in which eleven patients had both PET-CT and CTA scans, the results were concordant in six but diverged in five, PET-CT found LVI undetected by CTA [37]. In another recent study, comparing these two imaging techniques face-to-face, PET was shown to have a higher positive predictive value [38].

The limitations of this study: a small cohort which does not allow showing other possible significant differences, a relative short follow-up period for some patients and only one investigator. The strengths of this study: clinical setting, only one investigator ensuring that all measurements were made in a similar manner with less risk of measurement errors, longitudinal, systematic clinical vascular evaluation and available TAB and imaging for all patients.

In conclusion, peripheral vascular assessment is a useful tool to monitor disease activity since normal to low-grade rise in inflammatory markers and absence of other subjective or objective findings does not exclude progress of vascular damage. Identification of LV-GCA patients is important since they apparently have a more complicated disease course, are in need of a tighter control, a customised follow-up and a heavier immunosuppressive treatment (Supplementary Table). The risk of over-treatment in this group would be low, in this study 13%.

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