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ORIGINAL RESEARCH

Reappraisal of large artery involvement in giant cell arteritis: a population-based cohort over 70 years

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ABSTRACT

Objective To evaluate the incidence and outcomes of large artery (LA) involvement among patients with giant cell arteritis (GCA) and to compare LA involvement to non-GCA patients.

Methods The study included Olmsted County, Minnesota, USA residents with incident GCA between 1950 and 2016 with follow-up through 31 December 2020, death or migration. A population-based age-matched/sex-matched comparator cohort without GCA was assembled. LA involvement included aortic aneurysm, dissection, stenosis in the aorta or its main branches diagnosed within 1 year prior to GCA or anytime afterwards. Cumulative incidence of LA involvement was estimated; Cox models were used.

Results The GCA cohort included 289 patients (77% females, 81% temporal artery biopsy positive), 106 with LA involvement.

Reported cumulative incidences of LA involvement in GCA at 15 years were 14.8%, 30.2% and 49.2% for 1950–1974, 1975–1999 and 2000–2016, respectively (HR 3.48, 95% CI 1.67 to 7.27 for 2000–2016 vs 1950–1974).

GCA patients had higher risk for LA involvement compared with non-GCA (HR 3.22, 95% CI 1.83 to 5.68 adjusted for age, sex, comorbidities). Thoracic aortic aneurysms were increased in GCA versus non GCA (HR 13.46, 95% CI 1.78 to 101.98) but not abdominal (HR 1.08, 95% CI 0.33 to 3.55).

All-cause mortality in GCA patients improved over time (HR 0.62, 95% CI 0.41 to 0.93 in 2000–2016 vs 1950–1974) but remained significantly elevated in those with LA involvement (HR 1.89, 95% CI 1.39 to 2.56).

Conclusions LA involvement in GCA has increased over time. Patients with GCA have higher incidences of LA involvement compared with non-GCA including thoracic but not abdominal aneurysms. Mortality is increased in patients with GCA and LA involvement highlighting the need for continued surveillance.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Large artery involvement has been reported in patients with giant cell arteritis (GCA); however, the contemporary changes are not known and true risk of aneurysms remains unknown.

WHAT THIS STUDY ADDS

⇒ Any large artery involvement had 3.5-fold increase during 2000–2016 compared with 1950–1974 driven by 7-fold increase in large artery stenosis and a non-significant increase in aortic aneurysm/dissection.
⇒ 49.2% of GCA patients can have incident large artery complication if followed for 15 years.
⇒ GCA patients are at an increased risk for thoracic but not abdominal aortic aneurysm.
⇒ Mortality has increased in GCA patients with large artery involvement but fortunately the mortality has decreased in recent decades.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Continued screening for GCA patients for large artery complications if the initial evaluation was negative.
⇒ Thoracic aortic aneurysm could be attributed to GCA but not abdominal aortic aneurysm.

INTRODUCTION

Giant cell arteritis (GCA) is the most common form of systemic vasculitis in adults above the age of 50 years.[1] GCA has been identified as a risk factor for large artery (LA) involvement involving the aorta and its main branches.[2–4]

Interestingly, the epidemiology of GCA has been changing in recent years with decreasing incidence and mortality. However, the impact of this change on the incidence of LA involvement is not clear, especially with the increased use of imaging over the last few decades.[1 4–6]

Understanding the risk of LA involvement has also been challenging over the years, especially with conflicting reports on the risk of abdominal aortic aneurysm as well as the magnitude of risk for thoracic aortic aneurysm.[2–4 7] Moreover, given the advanced age of patients with GCA and the prevalence of atherosclerosis, it is difficult to quantify the true risk attributed to GCA and how much atherosclerosis contributes to the

radiographic findings in these patients.[2 3] The American College of Rheumatology (ACR) guidelines for management of GCA recommend screening patients for LA involvement at baseline; however, the utility and timing of repeat imaging are not clear if the initial imaging is negative.[8]

The aims of this study were to identify the incidence, time trends, risk factors and outcomes of LA involvement in patients with GCA, and, to compare LA incidence in patients with GCA diagnosed between 2000 and 2016 to an age-matched and sex-matched non-GCA cohort from the same population.

METHODS

This is a retrospective cohort study including all patients with an incident diagnosis of GCA in Olmsted County, Minnesota, USA during the period 1 January 1950–31 December 2016. The study was made possible using the resources of the Rochester Epidemiology Project (REP) which is a record data linkage system that includes all records for residents of Olmsted County, Minnesota, USA and provides access to both inpatient and outpatient records for all healthcare providers in Olmsted County, Minnesota, USA, therefore, making the population of Olmsted County well suited for population-based research.[9]

The patient cohort is described in detail elsewhere.[5] Briefly, patients were included in the study if they had clinical diagnosis of GCA by the treating physician and confirmed by a rheumatologist. Patients also fulfilled at least one of the following criteria:

- ≥3 out of 5 criteria points on the 1990 ACR classification criteria.[10]
- Age ≥50 years with elevated inflammatory markers (Erythrocyte sedimentation rate (ESR) ≥50 mm/hour or C-reactive protein (CRP) ≥10 mg/L) and clinical signs of GCA.
- Age ≥50 years with elevated inflammatory markers (ESR≥50 mm/hour or CRP≥10 mg/L) and with radiographic evidence of large-vessel vasculitis using either (CT angiography (CTA), MR angiography or positron emission tomography-computed tomography).

The GCA cohort was divided into three time intervals (1950–1974, 1975–1999 and 2000–2016) to study incidence trends over time.

Incident LA involvement was defined as aortic aneurysm, aortic dissection/rupture, stenosis of the aorta or any of its main branches diagnosed within 1 year prior to the diagnosis of GCA or anytime thereafter during the follow-up period.[3 4] Aortic aneurysm was defined as enlargement of the ascending aorta ≥4.5 cm or ≥3 in the abdominal aorta. LA stenosis was defined as narrowing of the aorta or any primary branch of the aorta as well as other arteries with a size greater than radial artery and included (innominate, subclavian, axillary, brachial, vertebral, basilar, common carotid, external and internal carotid, iliac, femoral and popliteal arteries). Coexistent aortic aneurysm and dissection was captured as aortic dissection. LA involvement had to be confirmed by radiological report (angiography, echocardiography, CT, MRI or ultrasonography) surgical pathology or autopsy.

To study the effect of increased imaging utilisation in the last two decades on detection of LA involvement, and, to evaluate contribution of atherosclerotic risk factors to LA involvement, a comparator cohort from the same population was assembled. The comparator cohort was designed to correspond with patients with incident GCA between 1 January 2000 and 31 December 2016. Additional details on the comparator cohort have been previously reported.[11] Each patient in the GCA cohort was age-matched and sex-matched to one subject without GCA from the same population. Each non-GCA subject was assigned an index date corresponding to the incidence date of their matched GCA patient. Three subjects in the comparator cohort later developed GCA; the last day of follow-up for these three patients was the incident date of GCA.

All subjects in both cohorts were followed till 31 December 2020, death or migration. Incident LA involvement was recorded using the same definitions in both cohorts.

The medical records for all subjects were manually reviewed, and information was abstracted in a standardised form to include all relevant clinical data for GCA diagnosis and medical comorbidities (hypertension, diabetes mellitus, hyperlipidaemia, stroke, transient ischaemic attacks, coronary artery disease and congestive heart failure) on the basis of physician diagnosis as documented in the medical records.

Descriptive statistics (mean with SD) were used to summarise patient characteristics. Comparisons between the groups were performed using χ^2 or rank-sum tests. The cumulative incidence of each LA involvement was estimated with adjustment for the competing risk of death. Cox models were used to assess the association of clinical characteristics with LA involvement. Time-dependent covariates were used to represent comorbidities that could develop during follow-up, as well as to assess the association of LA involvement with mortality. The distribution of survival following the date of LA involvement was estimated using the Kaplan-Meier method. The expected number of deaths was determined using the US population, according to the age, sex and calendar year of the cohort. Standardised mortality ratios (SMRs) were estimated as the ratio of the observed and expected number of deaths. Ninety-five per cent CIs for the SMRs were calculated assuming that the expected rates were fixed, and the observed rates followed a Poisson distribution. A $p<0.05$ was considered statistically significant for all analyses. Analyses were performed using SAS V.9.4 (SAS Institute) and R V.4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The GCA cohort

The GCA cohort included 289 patients with incident GCA in 1950–2016; majority were female (222, 77%). Mean age at diagnosis was 76.4 (SD 8.2) years, mean follow-up duration was 10.4 (SD 7.0) years. The mean age at diagnosis has increased significantly in the later cohort 2000–2016 compared with the earlier cohorts 1950–1974 and 1975–1999 (p=0.004). Temporal artery biopsy (TAB) was positive in 235 patients (81%). Further details are in table 1.

LA involvement in the GCA cohort

The GCA cohort included 106 patients with incident LA involvement during the follow-up period, the majority of these (75%) were found incidentally on imaging. A total of 55 patients developed incident LA stenosis, a total of 43 patients developed incident aortic aneurysm/

Table 1 Baseline characteristics for the incident giant cell arteritis (GCA) cohort between 1950 and 2016 in Olmsted County, Minnesota, USA

Baseline characteristics	1950–1974 (N=41)	1975–1999 (N=129)	2000–2016 (N=119)	Total (N=289)	P value
Mean (SD) age in years	73.3 (7.5)	76.2 (8.2)	77.8 (8.1)	76.4 (8.2)	0.004
Female	31 (76%)	103 (80%)	88 (74%)	222 (77%)	0.54
Ever smoker	6/13 (46%)	45/87 (52%)	29/80 (36%)	80/180 (44%)	0.13
Temporal artery biopsy result					0.004
Negative	2 (5%)	9 (7%)	24 (20%)	35 (12%)	
Positive	34 (83%)	114 (88%)	87 (73%)	235 (81%)	
No biopsy	5 (12%)	6 (5%)	8 (7%)	19 (7%)	
Method of GCA diagnosis					<0.001
Positive TAB	34 (83%)	114 (88%)	87 (73%)	235 (81%)	
Positive imaging for LVV without TAB or TAB negative	0 (0%)	0 (0%)	13 (11%)	13 (4%)	
Clinical diagnosis with criteria with TAB/Imaging negative or not done	7 (17%)	15 (12%)	19 (16%)	41 (14%)	
Mean (SD) months from onset of symptoms to diagnosis	1.4 (1.3)	1.8 (3.4)	1.8 (3.9)	1.8 (3.4)	0.50
Mean (SD) years from diagnosis to last follow-up	11.8 (8.0)	11.3 (8.1)	8.9 (4.7)	10.4 (7.0)	--
Headache	32/41 (78%)	92/128 (72%)	84/118 (71%)	208/287 (72%)	0.68
Jaw claudication	23/41 (56%)	50/128 (39%)	57/116 (49%)	130/285 (46%)	0.10
Scalp tenderness	13/34 (38%)	47/125 (38%)	61/115 (53%)	121/274 (44%)	0.042
PMR symptoms	9/41 (22%)	40/128 (31%)	34/118 (29%)	83/287 (29%)	0.52
Weight loss	10/41 (24%)	29/128 (23%)	34/116 (29%)	73/285 (26%)	0.48
Vision, permanent partial loss	5/41 (12%)	8/128 (6%)	6/118 (5%)	19/287 (7%)	0.28
Vision, permanent complete loss	1/41 (2%)	3/128 (2%)	2/118 (2%)	6/287 (2%)	0.93
Vascular bruit on examination	0/41 (0%)	5/123 (4%)	5/110 (5%)	10/274 (4%)	0.39
Arm claudication	0/41 (0%)	1/127 (1%)	2/117 (2%)	3/285 (1%)	0.60
Mean (SD) sedimentation rate	93.6 (20.1)	76.0 (30.0)	67.4 (31.2)	75.1 (30.4)	<0.001
Hypertension	8 (20%)	61 (47%)	87 (73%)	156 (54%)	<0.001
Hyperlipidaemia	7 (17%)	77 (60%)	94 (79%)	178 (62%)	<0.001
Diabetes mellitus	0 (0%)	5 (4%)	8 (7%)	13 (4%)	0.18
Stroke	3 (7%)	4 (3%)	10 (8%)	17 (6%)	0.19
Transient ischaemic attack	0 (0%)	6 (5%)	13 (11%)	19 (7%)	0.026
Congestive heart failure	3 (7%)	9 (7%)	9 (8%)	21 (7%)	0.98
Coronary artery disease	10 (24%)	26 (20%)	18 (15%)	54 (19%)	0.36

All values are number, % except if otherwise stated.

LVV, large-vessel vasculitis; PMR, polymyalgia rheumatica; TAB, temporal artery biopsy.

Table 2 Risk factors for any large artery involvement in patients with incident giant cell arteritis

Risk factor	HR* (95% CI) for any large artery involvement	HR* (95% CI) for aortic aneurysm/dissection	HR* (95% CI) for large artery stenosis
Age (years) per 10-year increase	1.07 (0.83 to 1.38)	1.35 (0.95 to 1.93)	0.97 (0.71 to 1.33)
Male	1.41 (0.90 to 2.21)	1.23 (0.65 to 2.33)	1.49 (0.85 to 2.62)
TAB positivity (reference: TAB negative)	0.38 (0.23 to 0.64)	0.89 (0.38 to 2.11)	0.26 (0.15 to 0.48)
Months from onset of symptoms to diagnosis	1.06 (1.02 to 1.11)	1.03 (0.96 to 1.11)	1.07 (1.01 to 1.12)
Ever smoker	1.77 (1.06 to 2.94)	1.61 (0.78 to 3.33)	1.77 (0.95 to 3.30)
Weight loss	1.70 (1.10 to 2.61)	1.15 (0.61 to 2.14)	2.15 (1.26 to 3.65)
Fatigue	1.71 (1.14 to 2.56)	1.71 (1.00 to 2.93)	1.29 (0.76 to 2.19)
Headache	0.62 (0.40 to 0.94)	0.72 (0.40 to 1.28)	0.53 (0.31 to 0.89)
Arm claudication	4.48 (1.07 to 18.75)	--	7.12 (1.67 to 30.47)
Bruit on physical examination	2.74 (1.18 to 6.35)	0.95 (0.23 to 3.92)	3.75 (1.48 to 9.51)
Hypertension†	2.03 (1.30 to 3.17)	1.22 (0.70 to 2.15)	3.33 (1.76 to 6.30)
Hyperlipidaemia†	2.08 (1.29 to 3.35)	2.12 (1.08 to 4.16)	2.11 (1.15 to 3.86)
Diabetes mellitus†	1.49 (0.79 to 2.80)	1.06 (0.42 to 2.68)	1.74 (0.78 to 3.86)
Stroke†	2.00 (1.14 to 3.53)	0.91 (0.39 to 2.16)	3.03 (1.56 to 5.86)
Transient ischaemic attack†	2.04 (1.19 to 3.52)	1.65 (0.80 to 3.42)	3.08 (1.67 to 5.70)
Congestive heart failure†	1.11 (0.63 to 1.96)	1.58 (0.82 to 3.01)	0.77 (0.32 to 1.86)
Coronary artery disease†	1.85 (1.21 to 2.82)	2.30 (1.35 to 3.93)	1.53 (0.87 to 2.69)

*Age and sex adjusted.
†Time-dependent covariate.
TAB, temporal artery biopsy.

dissection and 8 patients developed both concurrently (ie, within 12 months) following the incident LA involvement. Eight patients with either incident LA stenosis or aortic aneurysm/dissection developed the other type during follow-up.

There were a total of 64 GCA patients with reported LA stenosis in the entire cohort (56 patient had reported stenosis only, 3 patients had reported occlusion only and 5 patients had reported both stenosis and occlusion). Arterial occlusions included five patients with reported carotid/vertebral artery occlusion, two patients with femoral artery and one patient with subclavian artery occlusion. The most common reported sites of LA stenosis were internal carotid and/or vertebral arteries 36/61 (59%) and subclavian artery 23/61 (38%).

Predictors of LA involvement in the GCA cohort

Clinical predictors of LA involvement were studied using age-adjusted and sex-adjusted Cox models (table 2). Headache (Hazard ratio (HR) 0.62, 95% CI 0.40 to 0.94), TAB positivity (HR 0.38, 95% CI 0.23 to 0.64 vs TAB negative) were found to be negatively associated with the development of LA involvement. Ever smoking (HR 1.77, 95% CI 1.06 to 2.94), weight loss (HR 1.70, 95% CI 1.10 to 2.61), fatigue (HR 1.71, 95% CI 1.14 to 2.56), arm claudication (HR 4.48, 95% CI 1.07 to 18.75), bruit on physical examination (HR 2.74, 95% CI 1.18 to 6.35) and delayed diagnosis from onset of symptoms (HR per 1-month increase 1.06, 95% CI 1.02 to 1.11) were found to be positive predictors for the development of LA involvement among patients with GCA at diagnosis (table 2).

Limiting the age-adjusted and sex-adjusted Cox model to the follow-up time beginning 30 days after GCA incidence date revealed no significant difference in TAB positivity (HR 0.72, 95% CI 0.34 to 1.52), headache (HR 0.86, 95% CI 0.50 to 1.47) and jaw claudication (HR 0.96, 95% CI 0.61 to 1.51).

Medical comorbid conditions as time-dependent factors were also studied. Hypertension (HR 2.03, 95% CI 1.30 to 3.17), hyperlipidaemia (HR 2.08, 95% CI 1.29 to 3.35), stroke (HR 2.00, 95% CI 1.14 to 3.53), transient ischaemic attacks (HR 2.04, 95% CI 1.19 to 3.52) and coronary artery disease (HR 1.85, 95% CI 1.21 to 2.82) were found to be positive predictors for the development of LA involvement at GCA diagnosis (table 2). However, diabetes mellitus (HR 1.49, 95% CI 0.79 to 2.80), congestive heart failure (HR 1.11, 95% CI 0.63 to 1.96) and peripheral arterial disease (HR 1.04, 95% CI 0.45 to 2.44) were not significantly associated with the development of LA involvement (table 2).

LA incidence time trends in GCA

The cumulative incidence rates of LA involvement at 15 years after GCA incidence were 14.8% (95% CI 7.0% to 31.6%), 30.2% (95% CI 23.2% to 39.4%) and 49.2% (95% CI 39.3% to 61.7%) for 1950–1974, 1975–1999 and

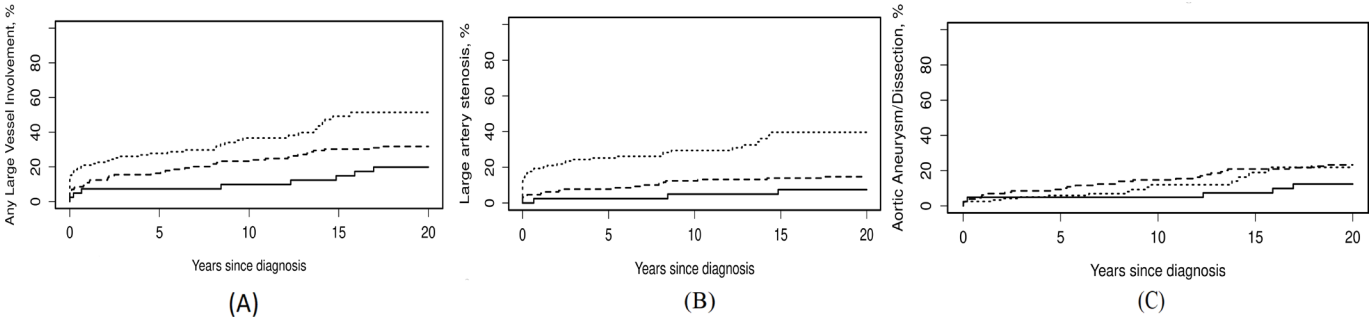

Figure 1 Cumulative incidence for time to any large artery involvement (A), large artery stenosis (B) and aortic aneurysm/dissection (C) within 1 year prior or any time after incidence date in patients with incident GCA in Olmsted County, Minnesota, USA adjusted for the competing risk of death by time period (1950–1974 is solid line, 1975–1999 is dashed line, 2000–2016 is dotted line). Incidence up to 1 year prior to incidence date was recorded as occurring at incidence. GCA, giant cell arteritis.

2000–2016, respectively. This reflected 3.5-fold increase in the time interval 2000–2016 (HR 3.48, 95% CI 1.67 to 7.27) and 2-fold increase in the time interval 1975–1999 (HR 1.95, 95% CI 0.95 to 4.00) compared with the earliest time interval 1950–1974 adjusted for age and sex (figure 1 and table 3).

The cumulative incidence rates of LA stenosis at 15 years after GCA incidence were 7.5% (95% CI 2.4% to 22.8%), 14.0% (95% CI 9.1% to 21.5%) and 39.7% (95% CI 30.4% to 51.7%) for 1950–1974, 1975–1999 and 2000–2016, respectively. Compared with 1950–1974 cohort, there was a 7-fold increase in LA stenosis for 2000–2016 (HR 7.78, 95% CI 2.34 to 25.89) and 2.5-fold increase for the 1975–1999 cohort (HR 2.60, 95% CI 0.77 to 8.77) (figure 1 and table 3).

The cumulative incidence rates of aortic aneurysm or dissection at 15 years were 7.4% (95% CI 2.4% to 22.4%), 20.9% (95% CI 14.9% to 29.3%) and 19.0% (95% CI 11.3% to 31.8%) for the 3 time intervals, respectively. While there was a trend towards an increase in incidence rates, these did not reach statistical significance (HR 1.25, 95% CI 0.50 to 3.14) for 2000–1016 vs 1950–1974 and (HR 1.66, 95% CI 0.73 to 3.76) for 1975–1999 vs 1950–1974 (figure 1 and table 3).

Risk of LA involvement in GCA patients compared with non-GCA

Incidence of LA involvement was also evaluated in a non-GCA cohort from the same geographical area and compared with patients with GCA diagnosed between 2000 and 2016. The comparator cohort included 119 subjects, mean age was 77.7 (SD 8.2) years, 74% female; mean follow-up was 7.7 (SD 4.9) years. Incident LA involvement occurred in 20 subjects in the comparator cohort.

The cumulative incidence rate for any LA involvement at 15 years was 49.2% (95% CI 39.3% to 61.7%) in the GCA patients compared with 19.2% (95% CI 12.5% to 29.4%) in the non-GCA comparator cohort (figure 2, table 3). The cumulative incidence rate for any LA stenosis at 15 years of follow-up was 39.7% (95% CI 30.4% to 51.7%) in the GCA patients compared with 13.9%

Table 3 Cumulative incidence rate of any large artery involvement, large artery stenosis and aortic aneurysm/dissection adjusted for the competing risk of death for patients with giant cell arteritis (GCA; 1950–2016) as well as non-GCA (2000–2016) in Olmsted County, Minnesota, USA

Time point	1950–1974: Estimate (95% CI)	1975–1999: Estimate (95% CI)	2000–2016: Estimate (95% CI)	Non-GCA 2000–2016: Estimate (95% CI)
Any large artery involvement				
5 years	7.3% (2.4% to 22.1%)	16.3% (11.0% to 24.1%)	27.8% (20.8% to 37.2%)	11.2% (6.7% to 18.7%)
10 years	9.8% (3.8% to 25.3%)	23.3% (17.0% to 31.9%)	36.6% (28.5% to 47.1%)	16.0% (10.2% to 25.1%)
15 years	14.8% (7.0% to 31.6%)	30.2% (23.2% to 39.4%)	49.2% (39.3% to 61.7%)	19.2% (12.5% to 29.4%)
Any large artery stenosis				
5 years	2.4% (0.3% to 17.3%)	7.8% (4.3% to 14.1%)	25.2% (18.5% to 34.4%)	5.9% (2.9% to 12.2%)
10 years	4.9% (1.3% to 19.6%)	12.4% (7.8% to 19.7%)	29.4% (22.1% to 39.2%)	10.8% (6.1% to 19.2%)
15 years	7.5% (2.4% to 22.8%)	14.0% (9.1% to 21.5%)	39.7% (30.4% to 51.7%)	13.9% (8.2% to 23.7%)
Aortic aneurysm/dissection				
5 years	4.9% (1.2% to 19.2%)	9.3% (5.4% to 16.0%)	5.9% (2.9% to 12.2%)	5.2% (2.4% to 11.4%)
10 years	4.9% (1.2% to 19.2%)	14.7% (9.7% to 22.4%)	12.0% (6.9% to 20.7%)	5.2% (2.4% to 11.4%)
15 years	7.4% (2.4% to 22.4%)	20.9% (14.9% to 29.3%)	19.0% (11.3% to 31.8%)	5.2% (2.4% to 11.4%)

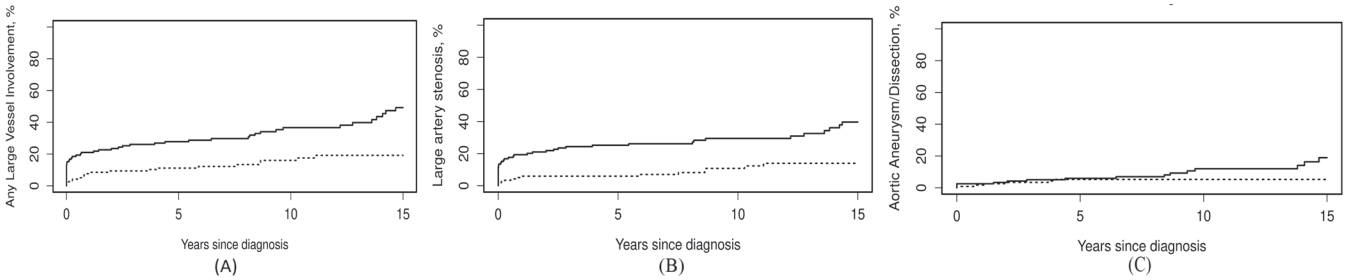

Figure 2 Cumulative incidence for time to any large artery involvement (A), large artery stenosis (B) and aortic aneurysm/dissection (C) within 1 year prior to index date or anytime thereafter among GCA patients (solid line) and non-GCA (dotted line) with incidence/index date 2000–2016 in Olmsted County, Minnesota, USA adjusted for the competing risk of death. GCA, giant cell arteritis.

(95% CI 8.2% to 23.7%) in the non-GCA comparator cohort (figure 2, table 3). The cumulative incidence rate for aortic aneurysm/dissection at 15 years of follow-up was 19.0% (95% CI 11.3% to 31.8%) in the GCA patients compared with 5.2% (95% CI 2.4% to 11.4%) in the non-GCA group (figure 2, table 3). When compared with the non-GCA cohort, patients with GCA had a higher risk of developing any LA involvement (HR 2.67, 95% CI 1.59 to 4.51), including LA stenosis (HR 2.98, 95% CI 1.62 to 5.48) and aortic aneurysm/dissection (HR 2.41, 95% CI 0.94 to 6.18) (table 4). Moreover, this risk persisted following additional adjustment for medical comorbidities including hypertension, hyperlipidaemia, diabetes mellitus, stroke and congestive heart failure (any LA involvement HR 3.22, 95% CI 1.83 to 5.68, LA stenosis HR 4.20, 95% CI 2.16 to 8.16 and aortic aneurysm/dissection HR 1.86, 95% CI 0.71 to 4.88) (table 4).

Aortic aneurysm/dissection was identified in 16 patients with GCA and 6 non-GCA, Thoracic aortic aneurysm in 15 patients (94%) with GCA and 1 patient (17%) without GCA whereas abdominal aortic aneurysm was identified in 6 GCA patients (38%) and 5 non-GCA (83%). LA stenosis was identified in 40 patients with GCA compared with 14 patients in the non-GCA group. Subclavian stenosis was noted in 17 GCA patients (43%) compared with 1 non-GCA (7%), axillary artery stenosis was identified in 9 GCA patients (23%) and none in non-GCA (online supplemental table 1). The risk for thoracic aortic aneurysm was significantly higher in patients with GCA (HR 13.46, 95% CI 1.78 to 101.98) compared with non-GCA subjects. However, the risk for abdominal aortic aneurysm was not significantly increased in GCA (HR 1.08, 95% CI 0.33 to 3.55).

Table 4 Risk for large artery involvement in patients with giant cell arteritis (GCA) compared with non-GCA comparators with incidence/index date between 2000 and 2016 in Olmsted County, Minnesota, USA

Type of large artery involvement	HR (95% CI)*	HR (95% CI)†
Any large artery involvement	2.67 (1.59 to 4.51)	3.22 (1.83 to 5.68)
Large artery stenosis	2.98 (1.62 to 5.48)	4.20 (2.16 to 8.16)
Aortic aneurysm/dissection	2.41 (0.94 to 6.18)	1.86 (0.71 to 4.88)
Thoracic aneurysm	13.46 (1.78 to 101.98)	‡
Abdominal aneurysm	1.08 (0.33 to 3.55)	‡

*Age and sex adjusted.
†Adjusted for age, sex, hypertension, hyperlipidaemia, diabetes mellitus, stroke, heart failure. Comorbid conditions were analysed as time-dependent variables.
‡Numbers were small for comparison.

Outcomes and mortality in the GCA cohort

During the follow-up period, eight patients underwent surgery for LA involvement. Six patients underwent ascending aortic aneurysm repair with pathology from the resected specimens showing active inflammation in 4 patients (66%). One patient underwent surgery for abdominal aortic aneurysm; however, histopathology evaluation was not available. One patient underwent carotid artery surgery with graft placement and active inflammation was reported on pathology. The cumulative incidence of aortic surgery at 15 years of follow-up was 2.9% (95% CI 1.5% to 5.8%)

GCA patients with LA involvement had increased risk of all-cause mortality compared with patients with GCA without LA involvement; HR 1.89, 95% CI 1.39 to 2.56 for any LA involvement, HR 1.60, 95% CI 1.12 to 2.29) for LA stenosis and HR 2.06, 95% CI 1.44 to 2.96 for aortic aneurysm/dissection. Survival analysis revealed SMR 1.55 (95% CI 1.23 to 1.93) for GCA patients with any LA involvement while SMR for GCA patients with LA stenosis was 1.28 (95% CI 0.93 to 1.72) and SMR for GCA patients with aortic aneurysm/dissection was 2.05 (95% CI 1.53 to 2.69) compared with the general US population (figure 3).

Among patients with LA involvement, patients who developed aortic dissection were at highest risk of death (HR 11.44, 95% CI 5.12 to 25.61) compared with those with LA stenosis, whereas those with aortic aneurysm demonstrated a modest elevated risk that did not reach statistical significance compared with those with LA

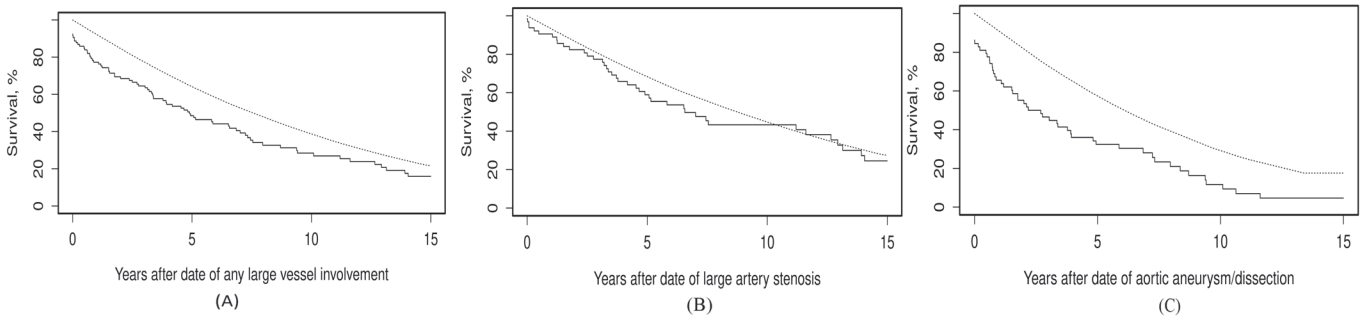

Figure 3 Survival in patients with GCA (solid line) who develop any large artery involvement (A), large artery stenosis (B) or aortic aneurysm/dissection (C) compared with the general US population (dotted line). Standardised mortality ratios (95% CIs) were 1.55 (1.23 to 1.93) for any large artery involvement, 1.28 (0.93 to 1.72) for large artery stenosis and 2.05 (1.53 to 2.69) for aortic aneurysm/dissection. GCA, giant cell arteritis.

stenosis (HR 1.50, 95% CI 0.90 to 2.49) when adjusted for age at incidence of LA involvement, sex and year of GCA diagnosis.

Among patients with GCA, LA involvement was a significant predictor of the following causes of mortality: respiratory illness (HR 4.57, 95% CI 1.80 to 11.58) and disease of the circulatory system (HR 2.64, 95% CI 1.69 to 4.11), but not the following causes: neoplasms (HR 1.22, 95% CI 0.39 to 3.87), neurological disorders (HR 1.10, 95% CI 0.32 to 3.77) and cognitive/mental conditions (HR 0.77, 95% CI 0.22 to 2.77) (table 5).

Overall mortality among patients with GCA has decreased, regardless of the presence of LA involvement with a 38% reduction for those diagnosed in 2000–2016 vs 1950–1974 (HR 0.62, 95% CI 0.41 to 0.93), and a 14% reduction for those diagnosed in 1975–1999 vs 1950–1974 (HR 0.86, 95% CI 0.60 to 1.23). This finding was also applicable to the subset of patients with LA involvement (adjusted for age and sex at LA involvement) with 62% decrease in mortality after LA involvement for those who were diagnosed with GCA between 2000 and 2016 vs 1950 and 1974 (HR 0.38, 95% CI 0.18 to 0.83) and a non-significant 35% decrease in mortality after LA involvement in those diagnosed with GCA between 1975 and 1999 vs 1950 and 1974 (HR 0.65, 95% CI 0.31 to 1.38).

DISCUSSION

Our study found the incidence of LA involvement in GCA has been increasing over time. This increased incidence has been driven predominantly by a 7-fold increase in LA stenosis for patients diagnosed in 2000–2016 compared with 1950–1974.

The frequency of any LA involvement with a cumulative incidence of 49% by 15 years demonstrates a need to continue screening GCA patients for LA involvement throughout the follow-up period, even if the initial evaluation was negative.

Interestingly, the epidemiology of GCA is changing with declining incidence rates in general[5]; however, it is not clear if the epidemiology of LA involvement is related to a change of the disease phenotype itself or secondary to the increased awareness of LA involvement as well as increased use of imaging techniques as part of the clinical evaluation for patients with GCA. The mean age at onset was has increased significantly in the later cohort 2000–2016 compared with earlier time intervals, this is in line with previous reports from Europe and the USA.[12]

Predictors for LA involvement at incidence identified in this study included: systemic symptoms, arm claudication, as well as traditional risk factors for atherosclerosis

Table 5 Associations between large artery involvement and mortality (all cause and cause-specific) in patients with incident giant cell arteritis (GCA) in Olmsted County, Minnesota, USA

Cause of death	No of deaths	Type of large artery involvement*	HR† (95% CI)
All causes	226	Large artery stenosis	1.60 (1.12 to 2.29)
All causes	226	Aortic aneurysm/dissection	2.06 (1.44 to 2.96)
All causes	226	Any large artery involvement	1.89 (1.39 to 2.56)
Circulatory system	106	Any large artery involvement	2.64 (1.69 to 4.11)
Respiratory system	25	Any large artery involvement	4.57 (1.80 to 11.58)
Neoplasms	22	Any large artery involvement	1.22 (0.39 to 3.87)
Mental	19	Any large artery involvement	0.77 (0.22 to 2.77)
Nervous system	14	Any large artery involvement	1.10 (0.32 to 3.77)

*Time-dependent covariate.
†Adjusted for age, sex and calendar year of GCA diagnosis.

(smoking, coronary artery disease, hypertension, hyperlipidaemia and stroke). On the other hand, cranial symptoms were negatively associated with large-vessel involvement, which has been previously reported.[4 7 13–16] However, the increased risk of LA involvement in patients who were biopsy negative and those without cranial symptoms was limited to initial presentation and no increased risk was noted beginning 30 days after GCA incidence date.

Whether this increased incidence of LA stenosis is due to atherosclerosis or the disease itself was previously not clear. Our study compared non-GCA cohort from the same population to elucidate this. While the risk factors for LA involvement in the GCA cohort included traditional risk factors for atherosclerosis (coronary artery disease, hypertension, hyperlipidaemia, stroke and transient ischaemic attacks), even after adjusting for these risk factors, patients with GCA had an increased risk of LA involvement suggesting a large attribution from the disease itself.

During follow-up, GCA patients had aortic surgeries which revealed inflammation in 4/6 patients (66%) which is similar to a previous report of active inflammation in 4/7 patients with available histopathology who underwent aortic aneurysm surgery.[15] Moreover, carotid artery inflammation was noted in one patient who underwent surgery. This has been previously reported in the literature and further reinforces that, at least in some patients, LA involvement is secondary to vasculitis rather than to atherosclerosis.[17]

GCA was found to be a significant risk factor for thoracic aortic aneurysm (HR 13.46, 95% CI 1.78 to 101.98) but not abdominal aortic aneurysm. This is different from a previous landmark report from Olmsted County[2] that reported a 17-fold increase in risk for thoracic aortic aneurysm and a 2.5-fold increased risk for abdominal aortic aneurysm. The previous study used reference studies to calculate the risk which may have overestimated the risk of aneurysms. The magnitude of risk for thoracic aortic aneurysm is higher than reported in the UK (HR 1.92, 95% CI 1.52 to 2.41) based on International Classification of Diseases (ICD) coding which has its inherent limitations; moreover, the UK study grouped both thoracic aortic aneurysm and abdominal aortic aneurysm together which may have attenuated the risk of thoracic aortic aneurysm.[7] More recently, a population-based study from Denmark identified a similar risk (RR 11.2, 95% CI 7.41 to 16.9) for thoracic aortic aneurysm in patients with GCA. Concordant with our findings, the Danish study did not find a significant risk for abdominal aortic aneurysm (RR 1.04, 95% CI 0.83 to 1.32).[16] The most common site of aortic aneurysm was in the thoracic area which is in line with previous reports.[13 18 19] Moreover, the most common sites for stenosis were the subclavian and axillary arteries which is similar to previous reports both in retrospective studies as well as in prospective studies.[13 15 18 20]

All-cause mortality was increased in patients with LA involvement, which aligns with a previous report of increased all-cause mortality in GCA patients.[4] Interestingly, mortality in patients with LA involvement has been decreasing over time. This could reflect identification of milder involvement due to more frequent imaging or it could reflect a decrease in mortality trends among GCA patients in general. Decreasing mortality rates among patients with GCA have been reported.[6 21 22] LA involvement has been associated with an increased mortality.[20 22] Interestingly, higher mortality rates were reported among biopsy negative GCA patients in Denmark[23] which is a risk factor for LA involvement so it is possible that the increased mortality in the Danish study may be related to an added effect of LA involvement. Moreover, LA involvement was associated with reduced survival in a population-based study from Italy.[24]

Cause-specific mortality showed death from cardiovascular causes as the most common cause of death followed by disease of the pulmonary system. This is similar to previous reports from France,[22] Denmark[23] and the UK[25] which listed cardiovascular disease as the most common cause of death. Interestingly, all the previous studies—including this study—reported significant risk for both (cardiovascular system and pulmonary system) but the magnitude of risk seemed to differ, and this is probably secondary to the difference in the study design and ascertainment of the cause of death among these different studies.

The strengths of this study are the population-based design as well as the use of the REP which ensures capturing all records for the patient's both in the inpatient and outpatient setting. All the patients' records were manually reviewed including radiology reports to ascertain the diagnosis of GCA as well as LA involvement and minimise false positive results compared with other studies that rely on ICD coding. A limitation of the study would be the relatively small sample size compared with other database studies. However, with database-based studies, accuracy in identifying the disease and outcomes becomes challenging. Another limitation would be inherently related to the retrospective nature of the study and the reliance on physician documentation and available data in the medical charts for the patients.

It is worth noting that multiple factors have contributed to the rate of detection of LA involvement over the decades including the increase in the sensitivity of imaging technology (eg, chest X-ray vs CTA for detection of aneurysm), less invasive imaging (eg, catheter angiogram vs CTA to detect aortic branch stenosis) as well as an overall increase in the use of these modalities. Moreover, changes in physician practice over time and increased awareness of LA involvement may have also contributed to the increase in reported LA involvement in the recent cohort. In particular, carotid and/or vertebral artery disease was the predominant type of LA stenosis; and incidental detection of atherosclerosis at these locations may be confounding our results. Moreover, during the

early decades of our study cohort, these imaging modalities were not available, and therefore, we would have underestimated the frequency of these findings in our earlier patients. All these factors have thus limited our ability to provide accurate screening recommendations for LA involvement.

In conclusion, the incidence of LA involvement has been increasing over time; primarily driven by an increase in LA stenosis that may be due to increased use of imaging and improved imaging techniques. Systemic symptoms, smoking and extremity claudication were associated with LA involvement while cranial symptoms were protective. All-cause mortality is higher in patients with GCA with any LA involvement and is highest in those with aortic dissection. Even after adjusting for comorbid conditions, the risk of LA involvement was higher among GCA patients compared with non-GCA patients. Compared with the general population, GCA patients are at an increased risk for developing thoracic but not abdominal aortic aneurysm. GCA patients for whom initial imaging evaluation was negative for LA involvement will benefit from rescreening during their follow-up especially since LA involvement is associated with increased risk of mortality however optimal timing and imaging modality for repeat screening is not currently known and further studies especially prospective ones would be needed.

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