The association of vascular risk factors to visual loss in giant cell arteritis

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Abstract

Objective

Blindness is a recognised complication of giant cell arteritis (GCA); however the frequency and risk factors for this complication have not been firmly established. This study examined the incidence and determinants of blindness in patients with GCA using a large international cohort.

Methods

The analysis was conducted among subjects recruited into the Diagnosis and Classification Criteria in Vasculitis Study (DCAVS). The study captures consecutive patients presenting to clinic-based physicians. New onset blindness was assessed six months after diagnosis by completion of the Vasculitis Damage Index (VDI). Logistic regression analysis was used to assess the association between blindness and clinical variables.

Results

Of 433 patients with GCA from 26 countries, 7.9% presented with blindness in at least one eye at six months. Risk factors identified at baseline for blindness at six months were identified and included prevalent stroke (OR = 4.47, 95% CI: 1.30 to 15.41), and peripheral vascular disease (OR = 10.44, 95% CI: 2.94 to 37.03).

Conclusion

This is the largest study to date of subjects with incident GCA and confirms that blindness remains a common complication of disease and is associated with established vascular disease.

Trial registration: American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Diagnostic and Classification Criteria for Primary Systemic Vasculitis (DCVAS), https://clinicaltrials.gov/ct2/show/NCT01066208, ClinicalTrials.gov Identifier: NCT01066208.

Introduction

Giant cell arteritis (GCA) is the commonest form of large vessel vasculitis, with an estimated annual incidence of up to 32.8 per 100,000 individuals > 50 years old (1). Blindness is a well-recognised complication of GCA; however, information to date on the occurrence of visual loss in GCA is inconsistent and difficult to interpret. Previous studies have been conducted in small, selected, hospital-based patient series using different definitions of disease and clinical outcome resulting in imprecise estimates of risk, ranging from 2.9% to 66.2% (2, 3). Registry-based surveys have involved larger sample sizes but include less precise clinical detail.

Prompt treatment of patients with GCA with glucocorticoids may prevent visual loss but rarely reverses established changes (4) and better understanding is needed of the factors which place subjects at particular risk at the time they first present. Studies have implicated pre-existing vascular disease as a potential risk factor for subsequent visual loss in GCA (5-9). However considerable uncertainty remains as no single vascular risk factor has been reported consistently.

In this analysis we examine the rate of visual loss in the Diagnostic and Classification Criteria in Vasculitis Study (DCVAS), a large international cohort of well characterised patients with GCA (10). We examine the potential risk factors for blindness and focus on the association of vascular disease with ophthalmologic outcomes in GCA.

Patients and Methods

Setting

DCVAS was set-up in 2010 and recruits patients from 129 sites worldwide. The purpose of DCVAS is to develop and validate diagnostic and classification criteria for systemic vasculitis for use in daily clinical practice and in clinical trials. Physicians recruit patients with diagnoses of vasculitis or comparator conditions at the time of diagnosis. Information collected includes clinical, serological, pathological and radiological data.

Case Ascertainment - GCA Definition

As part of the DCVAS protocol, the examining physician was required to submit an assessment of their level of diagnostic certainty (very certain, ≥75%; moderately certain, 50-74%; uncertain, 25-49%; very uncertain, <25%) for each participant. Musculoskeletal features were also recorded but not whether patients had a prior diagnosis of polymyalgia rheumatica. Patients were included in the present analysis if they had a new baseline diagnosis of GCA (i.e. not relapsing disease) which was confirmed after six months with a confidence level of ≥75%. Also available were the results of temporal artery biopsy (TAB) to allow patients to be classified using the 1990 ACR criteria set for GCA (11). A positive TAB was defined as the presence of inflammatory cell infiltrate and / or presence of giant cells.

Definition of Blindness

The occurrence of new onset blindness at six months was assessed using the Vasculitis Damage Index (VDI) (12) which defines blindness in one or both eyes as complete loss of vision. Also recorded at baseline were data on ophthalmic features (amaurosis fugax – transient monocular blindness, sudden ongoing visual loss – loss of vision either visual field

defect or blindness, blurred vision, or diplopia – double vision). VDI also records diplopia and visual impairment as a single item. This was not included as a primary outcome measures due to the lack of consistency in definition.

Previous medical history

The DCVAS protocol records for all patient the previous history of medical conditions present before the onset of the current illness. Conditions specifically documented include: coronary heart disease, heart failure, peripheral vascular disease, hypertension requiring medication, chronic obstructive pulmonary disease, asthma, diabetes mellitus, cerebrovascular accident, dyslipidaemia and malignancy. These diagnoses were defined as, in common with many large registry datasets, a physician recorded entry in the patients' care record.

Statistical Approach

Descriptive statistics were used to assess patient characteristics, with standard nonparametric tests used to assess differences between groups. Previous publications have found an association between laboratory markers and subsequent blindness including relatively lower inflammatory markers, anaemia and thrombocytosis (5, 6, 13). For these reasons inflammatory markers: Erythrocyte Sedimentation Rate (ESR, C - reactive protein (CRP), and haematological tests: anaemia – haemoglobin (Hb) <100 g/L and platelets > 500 x 10^9/L were assessed for their association with subsequent blindness

Previous data suggested a relationship between prior vascular disease and ischaemic complications in GCA. A logistic regression analysis was applied to examine the strength of the association between vascular risk factors with blindness at six months recorded as odds rations (OR) with 95% confidence intervals (CI). In a sensitivity analysis, the models were

recalculated firstly using the 1990 ACR criteria set and secondly positive temporal artery biopsy findings to define GCA diagnosis.

Statistical analysis was carried out using STATA version 12 (StataCorp LP, Texas).

Results

Of the 715 patients recruited into DCVAS by December 30, 2014 with complete data, 433 were considered to have GCA with ≥75% diagnostic certainty at six months; 404 fulfilled the 1990 ACR criteria for GCA; and 235 had a positive TAB. The patients were in the main (95.6%) Caucasians from Europe or North America (baseline characteristics - Table 1). Six months after diagnosis, 34 (7.9%) patients had monocular blindness, of whom 3 (0.7%) had binocular blindness (no statistical significant difference in the rate of blindness between men and women).

Thirty-one of the patients that had blindness recorded at six months (22 women and 12 men) had presented with symptoms of sudden visual loss, with only two patients without visual disturbance (including amaurosis fugax, visual loss, blurred vision or diplopia) at baseline being declared blind at six months. The visual manifestations of disease for all patients with GCA at presentation included: blurred vision in 98 (22.6%), sudden visual loss in 70 (16.2%), diplopia in 51 (11.8%), amaurosis fugax in 33 (7.6%), and red eyes in nine (2.1%). As expected, blindness at six months occurred more frequently in those who presented with visual symptoms. Of those with sudden visual loss at presentation, 44.3% (31/70) were blind at six months as assessed on the VDI; of those with no recorded visual loss at presentation, 0.8% (3/363) were recorded as being blind at the six month review. Patients who developed blindness had a lower CRP at presentation; however, no other clinical feature of GCA itself was associated significantly with blindness at 6 months.

Table 2 shows the results of logistic regression analysis examining associations between potential vascular risk factors assessed at baseline and blindness (adjusted for age and sex).

Factors positively associated with blindness at six months included i) a prior history of cerebrovascular accident (CVA) (OR = 4.47, 95% CI: 1.30 to 15.41), and ii) peripheral vascular disease (PVD) (OR = 10.44, CI: 2.94 to 37.03). There was no association between baseline laboratory findings and blindness.

In the sensitivity analysis the findings were largely unchanged. The rates of blindness in those meeting the 1990 ACR criteria and those with a positive TAB were 7.4% and 9.8%, respectively. The associations between PVD and CVA remained statistically significant with positive associations for blindness at six months (for PVD, ACR cases OR = 9.40, (2.14 to 41.34), TAB positive cases OR = 9.22, (1.56 to 54.70), for CVA, ACR cases OR = 5.29, (95% CI 1.39 to 20.07), TAB positive cases OR = 4.02, (0.89 to 18.16)). The association between prevalent diabetes mellitus and blindness reached statistical significance for those cases defined by positive TAB (4.28, CI: 1.42 to 12.92) but not the cases defined by 1990 ACR criteria (2.24, CI: 0.84 to 5.96).

Discussion

This large observational study demonstrates that blindness remains a major problem in GCA. Around one in twelve patients is blind in one eye by six months after diagnosis. Most patients who develop blindness do so by the time of their first assessment with only two patients without symptoms of visual disturbance suffering blindness at six months. These results re-emphasise the need for urgent referral and rapid institution of glucocorticoid therapy (14). Our analysis shows an association between blindness and peripheral vascular disease.

The rate of blindness identified in the present study is lower than the majority of published estimates, possibly reflecting our narrower and more stringent definition of blindness. It could be that more patients suffered visual loss since 70 patients were noted to have this complication at their baseline visit. However, data from the Mayo clinic published data on 204 cases of GCA from Rochester, Minnesota, USA over a 55-year period revealed patients 47 (23.0%) had visual symptoms, with seven (3.4%) suffering blindness in one eye (of whom two had bilateral blindness), which is lower than our estimate (15). Subsequently this same research group reported that 8.2% of patients with GCA had permanent visual loss attributed to their vasculitis; these newer data are more consistent with our current estimate (16). Our estimate is higher than the 2.9% reported in the register-based study conducted by Mollan *et al.*(2), interpretation of which is limited both by the fact that the cases were identified though hospital episodes, and that classification criteria were not applied, potentially leading to an underestimate of the rate of blindness in those with GCA. In addition care episodes, rather than individual patient records were used leading to the potential for double or multiple counting.

In keeping with other studies, a lower mean inflammatory marker result was noted in those with blindness, which reached statistical significance for CRP but not for ESR. It may be that patients with lower inflammatory markers at baseline assessment are at greater risk of blindness due to prior inadequate treatment with glucocorticoids, equally it may be a factor that contributes to diagnostic delay, or reflect a propensity for inflammation in smaller vessels. We also identified prior peripheral vascular disease as a risk factor for blindness in patients with GCA. Previous studies have implicated hypertension, a past history of ischaemic heart disease, thrombocytosis, constitutional symptoms, and low inflammatory response as potential risks for blindness (5, 6, 17). While reports have been inconsistent and many of these factors were not confirmed in the present study, taken together these findings suggest a potential role of endothelial dysfunction in both the development of GCA and its ischaemic complications. The increased risk of CVD following a diagnosis of GCA is also consistent with this hypothesis (18).

A strength of this study is its size: 433 new cases of GCA were included, each of which had a systematic structured assessment that included presenting features, comorbidities, and outcome at six months. Outcomes were assessed by the VDI, a validated means of recording permanent damage arising from vasculitis or its treatment.

Limitations of the study include referral bias due to the fact that it was clinic, rather than population-based. However, our sample was not selected from an individual specialty or specialist centre, providing potentially greater generalisability than prior single-centre studies. A formal ophthalmological assessment was not carried out routinely as part of DCVAS and the study protocol does not include additional review of the care records. Other limitations include the descriptions used for visual change and loss within the DCVAS case

report form, which we were concerned may not have been uniformly applied. We therefore chose to use the most definitive outcome measure available, i.e., complete loss of vision in the affected eye.

It is difficult to comment in full on the detailed causal pathways involved in those whose symptoms evolved over the six months of follow-up, but we note that only two patients without any visual disturbance were declared blind in one eye at six months. Our analysis of obesity and blindness needs to be treated with caution due to the relatively high proportion of missing values for BMI in this dataset. We do not have information regarding the initial dose or route or timing of glucocorticoid therapy or anti-platelets such as aspirin. We do note however, that recent database studies in GCA (18, 19) have not included glucocorticoid treatment as a separate covariate, because their use is advised as the standard management for GCA (20), and it was therefore not considered possible to separate the effect of treatment and disease. This is the largest study to date of visual loss in cases of clinically-confirmed GCA and provides a robust estimate of blindness associated with a diagnoses of GCA. Blindness, both monocular and binocular, remains a major problem in GCA and this study points to the need to be especially vigilant of this outcome in patients with a higher conventional vascular risk.

Key Messages

- Data from 26 countries reveals 7.9% of patients with GCA are blind within six months.
- Prior history of peripheral vascular disease and stroke is associated with greatest risk of blindness.

Contributions: MY carried out the analysis and wrote the draft of the manuscript. AJM commented on the analysis and carried out re-drafting of the manuscript with MY. JR commented on drafts of the manuscript. AC is the research co-ordinator for the DCVAS study and carried out database searches and produced the dataset. PAM, RAL and RAW and the main investigators for the DCVAS study and have been involved in the design, set-up, ethical approval, recruitment of the DCVAS study (and are custodians of the data) they have all commented on the manuscript drafts.

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Table 1. Clinical Features at baseline of patients with giant cell arteritis

Clinical Features	Physician Diagnosis of GCA at 6 months (>75% certainty) n=433		
	Blind at six months (n=34)	Not blind at six months (n=399)	p value*
Age at diagnosis (median, years)	74.9	73.0	0.073
Male (%)	12 (35.3)	133 (33.3)	0.816
New-onset headache	23 (67.7)	282 (70.7)	0.710
Any visual symptom (%)	32 (94.1)	154 (38.6)	0.000
Jaw claudication (%)	13 (38.2)	163 (40.9)	0.766
Tongue claudication (%)	3 (8.8)	16 (4.0)	0.188
Morning stiffness shoulders arms (%)	7 (20.6)	87 (21.8)	0.869
Morning stiffness hips/thighs (%)	5 (14.7)	69 (17.3)	0.700
Myalgia (%)	5 (14.7)	109 (27.3)	0.109
Fever (%)	3 (8.8)	68 (17.0)	0.214
Fatigue (%)	13 (38.2)	164 (41.1)	0.744
Weight loss (%)	12 (35.3)	138 (34.6)	0.934
Smoking Status			
Current (%)	4 (14.0)	56 (11.8)	0.741
Former (%)	9(31.1)	124 (26.5)	0.741
Never (%)	21 (54.9)	219 (61.8)	0.741
Comorbidities			
Coronary heart disease (%)	2 (5.9)	27 (6.8)	0.843
Heart failure (%)	0 (0.0)	9 (2.26)	0.376
Peripheral vascular disease (%)	5 (14.7)	6 (1.5)	0.000
Hypertension requiring therapy (%)	15 (44.1)	164 (41.1)	0.732
Diabetes mellitus (%)	7 (20.6)	33 (8.3)	0.017
Cerebrovascular accident (%)	4 (11.8)	10 (2.5)	0.003
Dyslipidaemia (%)	10 (29.4)	87 (21.8)	0.307
Chronic obstructive Pulmonary disease	0 (0.0)	24 (6.0)	0.141
Laboratory test results at presentation (%)			
Positive temporal artery biopsy	23 (67.7)	203 (50.9)	0.060
Median ESR mm/hr	65	70	0.620
Median CRP mg/L	46	64	0.025
Anaemia (Haemoglobin <100g/L) (%)	4 (11.8)	62 (15.5)	0.803
Thrombocytosis (platelets > 500 x 10^9/L) (%)	3 (8.8)	75 (18.8)	0.330

*p-value of difference between those who were subsequently declared blind in at least one eye versus those who were not; all calculated using the chi squared test except for median age at

diagnosis, ESR and CRP which was tested by the Mann-Whitney test. GCA: giant cell arteritis; ESR: erythrocyte sedimentation rate; CRP: C - reactive protein.

Table 2. Association between vascular disease factors assessed at presentation and blindness at 6 months.

Presenting features	Physician Diagnosis of GCA at 6 months (>75% certainty) n=433		1990 ACR Criteria cases n=404	TAB positive cases n=235
	Unadjusted OR, 95% CI	Adjusted* OR, 95% CI	Adjusted* OR, 95% CI	Adjusted* OR, 95% CI
BMI†	1.10, (1.01 to 1.19)	1.10, (1.02 to 1.20)	1.10, (1.00 to 1.21)	1.13, (1.00 to 1.28)
Smoking (ever vs never)	0.75, (0.37 to 1.55)	0.78, (0.36 to 1.68)	0.65, (0.28 to 1.54)	0.70, (0.26 to 1.84)
Cardiovascular disease at baseline	0.86, (0.20 to 3.79)	0.77, (0.17 to 3.45)	0.77, (0.16 to 3.58)	2.02, (0.38 to 10.78)
Diabetes at baseline	2.88, (1.16 to 7.10)	2.48, (0.98 to 6.25)	2.26, (0.82 to 6.17)	4.19, (1.39 to 12.67)
Stroke at baseline	5.19, (1.54 to 17.53)	4.47, (1.30 to 15.41)	5.29, (1.39 to 20.07)	4.02, (0.89 to 18.16)
Peripheral vascular disease at baseline	11.29, (3.25 to 39.23)	10.44, (2.94 to 37.03)	9.40, (2.14 to 41.34)	9.22, (1.56 to 54.70)
Hyperlipidaemia at baseline	1.49, (0.69 to 3.24)	1.45, (0.67 to 3.15)	1.43, (0.62 to 3.29)	2.20, (0.87 to 5.60)
Hypertension on medication at baseline	1.13, (0.56 to 2.29)	0.99, (0.48 to 2.03)	1.11, (0.51 to 2.39)	0.73, (0.30 to 1.79)

*Adjusted for age and sex. †Missing data for BMI (n = 131).

GCA: giant cell arteritis; OR: odds ration; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C -reactive protein.