# RISK FACTORS FOR VISUAL LOSS IN GIANT CELL ARTERITIS

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# ABSTRACT

## Background
Blindness is a recognised complication of giant cell arteritis (GCA); however the frequency and risk factors for this complication of disease have not been firmly established. This study examined the incidence and determinants of blindness in 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 rheumatologists. 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).

## Conclusions
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.

# INTRODUCTION

Giant cell arteritis (GCA) is the commonest form of large-vessel vasculitis, with an estimated annual incidence ranging from 12.7 to 36.7 per 100,000 individuals > 50 years old (1, 2). 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 outcomes and have produced a broad and imprecise range of estimates of risk, varying between 2.9% and 66.2% (3, 4). Registry-based surveys have involved larger samples sizes; however, the absence of accurate clinical detail generates uncertainty over the validity of these estimates.

Prompt treatment of patients with GCA with glucocorticoids may prevent visual loss but rarely reverses established pathological change in the eye (5) and there is need to better understand 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 (6-10). However considerable uncertainty remains as no single vascular risk factor has been reported consistently.

The recently-established international collaborative Diagnostic and Classification Criteria in Vasculitis Study (DCVAS) provides an opportunity to assess the rate of visual loss and the underlying risk factors in a large cohort of well characterised patients with GCA.

# PATIENTS AND METHODS

## Setting

DCVAS was set-up in 2010 and recruits patients from 129 sites worldwide. Physicians recruit patients with diagnoses of vasculitis or comparator conditions with an onset within the previous two years. 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. Patients were included in the present analysis if they had a baseline diagnosis of GCA by a submitting physician with a confidence level of ≥75%. Information was also available on the results of temporal artery biopsy and to allow patients to be classified using the 1990 ACR criteria set for GCA (11). A positive temporal artery biopsy was defined as the presence of inflammatory cell infiltrate and / or presence of giant cells.

## Definition of Blindness

Baseline data were extracted on ophthalmic features (amaurosis fugax, sudden ongoing visual loss, blurred vision in either eye, or diplopia) and the reasons for referral to secondary care. The occurrence of visual impairment at six months was assessed using the Vasculitis Damage Index (VDI) (12). Blindness was defined as complete loss of sight in the affected eye.

## Statistical Approach

Descriptive statistics were used to assess patient characteristics with standard nonparametric tests used to assess difference between groups. Logistic regression analysis was applied to examine the strength of the association between clinical variables with blindness at six months, recorded as odds rations (OR) with 95% confidence intervals (CI). In a sensitivity analysis, the models were recalculated using positive temporal artery biopsy and 1990 ACR criteria to define participant diagnoses. Statistical analysis was carried out using STATA version 12 (StataCorp LP, Texas).

# RESULTS

Of the 715 patients recruited into DCVAS by December 30, 2014, 433 were considered to have GCA with ≥75% diagnostic certainty at six months; 404 fulfilled the 1990 ACR criteria for GCA; and 235 had had a positive temporal artery biopsy. Baseline characteristics are shown in Table 1. Six months after diagnosis, 34 (7.9%) patients had monocular blindness, 3 (0.7%) of whom had binocular blindness. There were no statistically significant differences in the rate of blindness between men and women. Thirty-one of the patients that had blindness (22 women and 12 men) recorded at six months had presented with symptoms of sudden visual loss. 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 9 (2.1%). 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.

Table 2 shows the results of logistic regression analysis examining potential associations with blindness as recorded at 6 months using the VDI. The data were 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 suggestion that prevalent diabetes was also associated with blindness at six months; however the results failed to reach statistical significance.~~ There was no association between baseline laboratory findings and blindness at six months.

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 temporal artery biopsy were 7.4% and 9.8%, respectively. The associations between PVD and CVA remained statistically significant with positive associations for blindness at 6 months. The association between prevalent diabetes and blindness reached statistical significance for those cases defined by positive temporal artery biopsy (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).

**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 | | |
|---|---|---|---|
| | Male n=145 | Female n=288 | p value* |
| Age at diagnosis (median, years) | 73.9 | 72.9 | 0.863 |
| Amaurosis fugax (%) | 12 (8.3) | 21 (7.3) | 0.716 |
| Sudden visual loss ongoing (%) | 27 (18.6) | 43 (14.9) | 0.325 |
| Blurred vision either eye (%) | 35 (24.1) | 63 (21.9) | 0.595 |
| Diplopia (%) | 23 (15.9) | 28 (9.7) | 0.061 |
| Jaw claudication (%) | 56 (38.6) | 120 (41.7) | 0.543 |
| Tongue claudication (%) | 9 (6.2) | 10 (3.5) | 0.190 |
| Morning stiffness shoulders arms* (%) | 23 (15.9) | 71 (24.7) | 0.036 |
| Morning stiffness hips/thighs* (%) | 15 (10.3) | 59 (20.5) | 0.008 |
| Myalgia (%) | 38 (26.2) | 76 (26.4) | 0.968 |
| Fever (%) | 29 (20.0) | 42 (14.6) | 0.151 |
| Weight loss (%) | 49 (33.8) | 101 (35.1) | 0.792 |
| *Smoking Status** | | | |
| Current (%) | 25 (17.2) | 35 (12.2) | 0.148 |
| Former (%) | 70 (48.3) | 63 (21.9) | <0.001 |
| Never (%) | 50 (34.5) | 190 (66.0) | <0.001 |
| *Comorbidities* | | | |
| Coronary heart disease* (%) | 18 (12.4) | 11 (3.8) | 0.001 |
| Heart failure* (%) | 7 (4.8) | 2 (0.7) | 0.004 |
| Peripheral vascular disease (%) | 4 (2.8) | 7 (2.4) | 0.838 |
| Hypertension requiring therapy (%) | 60 (41.4) | 119 (41.3) | 0.990 |
| Diabetes mellitus* (%) | 19 (13.1) | 21 (7.3) | 0.049 |
| Cerebrovascular accident (%) | 4 (2.8) | 10 (3.5) | 0.692 |
| Dyslipidaemia (%) | 34 (23.5) | 63 (21.9) | 0.711 |
| Chronic obstructiv Pulmonary disease* | 15 (10.3) | 9 (3.1) | 0.002 |
| *Laboratory test results at presentation (%)* | | | |
| ESR greater than 70mm/hr (%) | 74 (51.0) | 153 (53.1) | 0.681 |
| CRP greater than 50mm/hr (%) | 93 (64.1) | 173 (60.0) | 0.412 |
| Anaemia (Haemoglobin <10g/dL) (%) | 16 (11.0) | 50 (17.4) | 0.170 |
| Thrombocytosis (platelets > 500 x $10^9$/L) (%) | 26 (17.9) | 52 (18.1) | 0.776 |

*p-value of difference between men and women; all calculated using the chi squared test except for median age at diagnosis which was tested by the Mann-Whitney test.

GCA: giant cell arteritis; ESR: erythrocyte sedimentation rate; CRP: c-reactive protein.

**Table 2.  Unadjusted and adjusted logistic regression analysis for blindness at 6 months associated with vascular disease variables.**

| Presenting features | Physician Diagnosis of GCA at 6 months (>75% certainty) n=433 | |
| --- | --- | --- |
| | Unadjusted OR, 95% CI | Adjusted* OR, 95% CI |
| Age | 1.04, (1.00 to 1.09) | 1.04, (1.00 to 1.09) |
| BMI† | 1.10, (1.01 to 1.19) | 1.10, (1.02 to 1.20) |
| Smoking (ever vs never) | 0.75, (0.37 to 1.55) | 0.78, (0.36 to 1.68) |
| Cardiovascular co-morbidity at baseline | 0.86, (0.20 to 3.79) | 0.77, (0.17 to 3.45) |
| Diabetes co-morbidity at baseline | 2.88, (1.16 to 7.10) | 2.48, (0.98 to 6.25) |
| Stroke co-morbidity at baseline | 5.19, (1.54 to 17.53) | 4.47, (1.30 to 15.41) |
| Peripheral vascular disease co-morbidity at baseline | 11.29, (3.25 to 39.23) | 10.44, (2.94 to 37.03) |
| Hyperlipidaemia co-morbidity at baseline | 1.49, (0.69 to 3.24) | 1.45, (0.67 to 3.15) |
| Hypertension co-morbidity at baseline | 1.13, (0.56 to 2.29) | 0.99, (0.48 to 2.03) |
| ESR >70mm/hr | 0.79, (0.39 to 1.60) | 0.79, (0.39 to 1.60) |
| CRP >50mg/L | 0.60, (0.30 to 1.22) | 0.57, (0.28 to 1.16) |
| Anaemia | 0.70, (0.25 to 1.99) | 0.78, (0.27 to 2.21) |
| Thrombocytosis | 0.42, (0.13 to 1.38) | 0.44, (0.13 to 1.48) |
| Weight loss | 1.03, (0.50 to 2.15) | 1.07, (0.51 to 2.23) |
| Fever | 0.47, (0.14 to 1.59) | 0.52, (0.15 to 1.75) |

*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.

# DISCUSSION

Results of this large observational study, demonstrate that blindness remains a major problem in GCA. Around one in twelve patients are blind in one eye by six months after diagnosis. Most patients who develop blindness do so by the time of their first assessment. These results re-emphasise the need for urgent referral and rapid institution of glucocorticoid therapy in patients (13). Our analysis also 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 definition of blindness as complete visual loss in one or both eyes. The Mayo clinic published data on 204 cases of GCA from Rochester, Minnesota, USA over a 55-year period. Of these patients 47 (23.0%) had visual symptoms, with 7 (3.4%) suffering blindness in one eye (of whom 2 had bilateral blindness), which is higher than our estimate (14). Our estimate is also higher than the 2.9% reported in the register-based study conducted by Mollan *et al.*(3), interpretation of which is limited by the fact that the cases were identified though hospital episodes. Rigorous classification criteria were not applied, potentially leading to an underestimate of the rate of blindness in those with GCA.

We 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 (6, 7, 15). While reports have been inconsistent and many of these factors were not been 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 (19, 20).

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 and not for other reasons.

Limitations of the study include the fact that it was clinic- rather than population-based and is thus susceptible to referral bias. However, our sample was not selected from an individual specialty or specialist centre, providing potentially greater generalizability than prior single-centre studies. Data directly from a detailed ophthalmological assessment was not recorded. However, the VDI was designed to capture data on visual impairment, blindness, and cataract formation which occurred specifically as a result of vasculitis or its therapy. Visual loss which developed for other reasons would not have been attributed to GCA. 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 and are, therefore, unable to state whether this had a bearing on the overall percentage of patients suffering blindness.

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 or binocular, remains a major problem in GCA and this study highlights the need for rapid referral and initiation of treatment.

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