

Concise Report

High incidence of severe ischaemic complications in patients with giant cell arteritis irrespective of platelet count and size, and platelet inhibition

C. T. Berger^{1,2}, M. Wolbers³, P. Meyer⁴, T. Daikeler^{1,5,*} and C. Hess^{1,2,*}

Objective. Vision loss and ischaemic stroke are feared complications in GCA. We investigated how platelet count and size and platelet inhibition with ASA relate to ischaemic complications in patients with GCA.

Methods. Charts of patients with GCA were retrospectively analysed. Jaw claudication, amaurosis fugax, blurred vision, ischaemic stroke and permanent visual loss were classified as 'ischaemic events'; ischaemic stroke and permanent visual loss were sub-grouped as 'severe ischaemic events'. The incidence of ischaemia and the association to the pre-defined covariates age, fever, ESR, platelet count and size and ASA treatment were assessed.

Results. Eighty-five patients (mean age 73 yrs, 60% women, 78% biopsy-proven) were included in the analysis. Of the 85 patients, 62 (73%) presented with ischaemic events, 29/85 patients (34%) with severe ischaemic events. At the time of diagnosis 22/85 patients (26%) were treated with ASA. Of these 22 patients, 15 (68%) presented with ischaemic events, 7/22 patients (32%) with severe ischaemic events. In multivariate analysis, neither platelet count nor size or ASA treatment were significantly associated with ischaemic or severe ischaemic events.

Conclusions. The incidence of severe ischaemic events in patients with GCA was high, irrespective of platelet count and size and established ASA treatment.

KEY WORDS: Giant cell arteritis, Ischaemia, Risk factors, Acetylsalicylic acid, Platelets.

Introduction

GCA is the most frequent of the vasculitis syndromes, affecting large arteries and being predominantly a disease of the elderly [1]. Patients typically present with constitutional symptoms, headache and a systemic inflammatory syndrome. Anterior ischaemic optic neuropathy (AION) with consecutive vision loss and ischaemic stroke are feared complications. Definite diagnosis relies on the presence of typical histological features in the biopsy of an affected artery. Identifying patients at risk for severe ischaemic events remains an unresolved issue. Older age, a low systemic inflammatory response and signs of ischaemia in absence of constitutional symptoms have all been suggested as independent risk factors for ischaemic damage [2–7]. Recently, the histopathological finding of occluding intima proliferation, and the presence and number of giant cells have been suggested as additional risk factors for ischaemic events [8, 9]. The pathogenic role of platelet aggregation in the development of irreversible ischaemic events in patients with GCA remains controversial [10–13]. Here we investigated how (i) platelet count and size [14] and (ii) established platelet inhibition with ASA are associated with ischaemic complications in a cohort of 85 patients with GCA.

Patients and methods

Study population, case definition and data collection

We conducted a retrospective chart analysis of patients with GCA. The study was approved by the local ethical committee (Basel, Switzerland). Patients were identified (i) via screening for histological diagnoses of GCA on temporal artery biopsy (TAB) between June 1997 and June 2007 at the Institute of Pathology of the University of Basel and (ii) by performing a computerized search for the diagnosis of GCA listed in demission letters issued from January 2003 through January 2007 for inpatients at the Department of Internal Medicine of the University Hospital Basel. Cases identified by this search were included in the study if they fulfilled ≥ 3 ACR classification criteria [15]. Patients with < 3 ACR criteria were included if on TAB histopathological features of GCA were present (inflammation, destruction of the internal elastic membrane, multinucleated giant cells) and additional firm evidence for GCA existed (e.g. AION or findings consistent with large vessel vasculitis on PET). Patients were excluded if data mandatory for disease classification were missing, or TAB was negative and < 3 ACR criteria were present.

Definitions of the ACR were used to classify clinical signs and symptoms. Weight loss of either > 2 kg over 1 month preceding diagnosis, or $> 10\%$ of the total body weight within 6 months preceding diagnosis was defined as being significant. As 'ischaemic events' we defined jaw claudication, amaurosis fugax, blurred vision in timely correlation to the diagnosis of GCA, AION and ischaemic stroke occurring within 2 weeks of diagnosis. The latter two (AION and ischaemic stroke) were sub-grouped as 'severe ischaemic events'. Normal values for ESR were defined as < 24 mm in the first hour (< 24 mm/1 h), normal values for platelet counts as $100\text{--}250 \times 10^9/l$. In all cases, a detailed chart review was performed (Table 1). Mean platelet volumes (MPVs) were measured using routine flow cytometric analysis (ADVIA 120 analyser, Siemens, Zürich, Switzerland). All available biopsies were re-reviewed and graded in a blinded manner by a senior

¹Department of Internal Medicine, ²Clinic for Transplantation Immunology and Nephrology, ³Basel Institute for Clinical Epidemiology and Biostatistics, ⁴Department of Ophthalmology and Institute of Pathology and ⁵Department of Rheumatology, University Hospital Basel, Basel, Switzerland.

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*T. Daikeler and C. Hess contributed equally to this work.

Correspondence to: C. T. Berger, Department of Internal Medicine, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland.
E-mail: bergerc@uhbs.ch

TABLE 1. Baseline characteristics and clinical presentation of the study population (N=85)

Age, mean \pm s.d. (range), yrs	73 \pm 8 (52–96)
Female gender, n (%)	51 (60)
ACR criteria, mean \pm s.d. (range)	3.9 \pm 0.9 (2–5)
TAB, done, n (%)	82 (97)
Positive TAB (of all patients), n (%)	66 (78)
Hb, mean \pm s.d. (range), g/l	123 \pm 16 (85–164)
MPV, mean \pm s.d. (range), fl	7.7 \pm 0.8 (6.1–9.5)
ESR, mean \pm s.d. (range), mm/1 h	68 \pm 28 (6–115)
Clinical symptoms at diagnosis, n (%)	
Headaches	74 (87)
PMR	53 (62)
Jaw claudication	45 (53)
Pathological temporal artery	42 (49)
Weight loss	29 (34)
Permanent vision loss	27 (32)
Scalp tenderness	27 (32)
Fever	18 (21)
Blurred vision	11 (13)
Amaurosis fugax	9 (11)
Stroke	2 (2)
One or more CVRF present, n (%)	67 (87)
Treatment at diagnosis, n (%)	
Prednisone	9 (11)
ASA	22 (26)
Oral anti-coagulation	7 (8)
Histopathological findings (N=80)	
Arterial lumen occlusion by intima hyperplasia, n (%)	
<50% (Grade 1)	16 (20)
50–75% (Grade 2)	24 (30)
>75% (Grade 3)	32 (40)
100% (Grade 4)	8 (10)
Presence/frequency of giant cells, n (%)	
Absent (Grade 0)	40 (50)
Rare (Grade 1)	26 (33)
Medium (Grade 2)	9 (11)
Numerous (Grade 3)	5 (6)

Hb: haemoglobin level, PTL: platelet count, CVRF: cardiovascular risk factors [i.e. arterial hypertension, n=60 (71%), diabetes mellitus type 2 n=12 (14%), hypercholesterolaemia n=17 (20%), smoking n=16 (19%)].

pathologist (P.M.). The degree of intimal proliferation-related maximal stenosis was graded as follows: Grade 1: <50%, Grade 2: 50–75%, Grade 3: >75% and Grade 4: complete luminal occlusion. The presence and number of giant cells was assessed semi-quantitatively (0: absent, 1: rare, 2: medium, 3: numerous) [8, 9].

Statistical methods

The association between ischaemic events (all and severe) and selected covariates was studied using simple and multiple logistic regression analysis. The following covariates were pre-defined: age, fever, ESR, platelet count, MPV and medication with ASA. In addition, the covariates ‘grade intimal hyperplasia’ and ‘grade of presence of giant cells’ were added to the model. Due to low sample size, we fitted only one parameter corresponding to a linear trend for ordinal covariates. Because of an almost perfect association of the semi-quantitative grade and the absolute maximal number of giant cells present on a biopsy, only the associations between the semi-quantitative grading and outcomes were explored. For reasons of efficiency and to avoid potential bias, we used multiple imputation of missing covariates for the multiple logistic regression analysis. All analyses were performed using R version 2.3.1 (R Foundation for Statistical Computing, Vienna, Austria) [16]. Multiple imputations were performed with the R package MICE [17].

Results

Screening histological data and demission letters we identified a total of 104 patients with suspected or definite diagnosis of GCA. Of these, 19 patients were excluded from analysis for the following reasons: 11/19 did not match inclusion criteria (negative TAB and ACR score \leq 2) or had a more probable alternative

diagnosis (2 \times Takayasu arteritis, 1 \times PAN), and in 8/19 data sets substantial portions of the clinical information (six patients) or laboratory values (two patients) were missing. On the other hand, one patient was included as ‘waiver’ despite fulfilling only two ACR criteria and being negative on TAB (78-yr old male, PMR, jaw claudication, ESR 68 mm/1 h, PET studies compatible with large-vessel vasculitis). MPV was missing for 18 of the 85 patients, platelet counts for four, information on medication with ASA for one patient, and for five patients biopsies were not available; none of the other covariates were missing for any patient. The clinical characteristics of the 85 patients included in this study and an overview of their clinical presentation at the time of diagnosis are summarized in Table 1. Intriguingly, at diagnosis 3/85 had an ESR <24 mm/1 h (i.e. a normal ESR) without prior treatment with corticosteroids. Two out of these three experienced AION, pointing out the importance of not excluding the possibility of GCA in patients presenting with normal ESR if other findings argue for this diagnosis. However, in both cases the distracting finding of a low ESR did not result in a diagnostic delay. Characteristics of the patients with low ESR without prior corticosteroid treatment are shown as Supplementary Table 1, available as supplementary data at *Rheumatology Online*.

Multiple regression analysis identified age as an independent risk factor for severe ischaemic complications [adjusted odds ratio (OR) = 2.72; 95% CI 1.26, 5.88; $P=0.01$], and showed that patients with fever (defined as a tympanic temperature >38.5°C) had a lower likelihood to present with any ischaemic event (adjusted OR = 0.23; 95% CI 0.06, 0.91; $P=0.04$) (Table 2). Jaw claudication (Fisher’s exact test: $P=0.04$), but not amaurosis fugax ($P=1$), was significantly associated with ‘severe ischaemic events’ in univariate analyses.

The retrospective nature of our data hinders a meaningful analysis of how the duration of jaw claudication and development of severe ischaemia are related. The overall incidence of ischaemic events was 73% (62/85 patients); the overall incidence of severe ischaemic events was 34% (29/85 patients). At the time of diagnosis, 22/85 patients (26%) were treated with ASA. In the ASA-treated subgroup, the incidence of ischaemic events was 68% (15/22 patients) and the incidence of severe ischaemic events was 32% (7/22 patients). Platelet counts were >250 $\times 10^9/l$ in 73/85 patients (86%) and >400 $\times 10^9/l$ in 45/85 patients (53%). Thrombopenia (platelet count <150 $\times 10^9/l$) was observed in only 2/85 patients (2%). No significant association of ischaemic events (all or severe) and platelet counts was detected (Table 2). Also, no significant correlation between an increased MPV and the occurrence of ischaemic events (all or severe) was detected (Table 2 and Fig. 1).

Overall, in biopsy-positive patients a trend towards a higher risk for ‘ischaemic events’ as well as for ‘severe ischaemic events’ was observed (56 vs 77%; unadjusted OR = 2.64; 95% CI 0.84, 8.30; $P=0.10$ and 19 vs 39%; unadjusted OR = 2.81; 95% CI 0.73, 10.85; $P=0.13$, respectively). The associations of the histopathological findings and ischaemic events are shown in Table 2. Assessing subgroups of ischaemic events, we found a significant association only for ‘jaw claudication’ with both the grade of arterial occlusion by intima proliferation ($P=0.01$) and the extent of the presence of giant cells ($P=0.046$). Of note, TAB in both patients with cerebral ischaemia showed >75% occlusion of the temporal artery due to intimal proliferation and numerous giant cells (Grade 3, maximal number of giant cells on a cross-section 5 and 8, respectively).

Discussion

The key finding of this study was a worrisome high incidence of severe ischaemic events (AION and stroke) in GCA patients treated with ASA—irrespective of their platelet count and size. This observation was made in a well-characterized cohort of 85

TABLE 2. Multiple logistic regression analysis of variables associated with any ischaemic events and severe ischaemic events

	Unadjusted ^a OR (95% CI)	P-value	Adjusted ^b OR (95% CI)	P-value
Ischaemic events				
Covariate				
Age (10yr increments)	1.31 (0.74–2.31)	0.36	1.12 (0.60–2.09)	0.72
Fever	0.26 (0.09–0.79)	0.02	0.23 (0.06–0.91)	0.04
ESR (increments of 10 mm/1 h)	0.93 (0.77–1.11)	0.42	0.91 (0.73–1.14)	0.42
PTL (increments of 10 ⁵ /mm ³)	1.11 (0.81–1.52)	0.52	1.20 (0.80–1.81)	0.39
MPV (fl)	1.04 (0.56–1.93)	0.91	0.80 (0.40–2.02)	0.80
ASA: yes	0.68 (0.23–1.99)	0.49	0.87 (0.25–3.08)	0.83
Intima proliferation (by +1 grade)	1.80 (1.01–3.20)	0.04	1.22 (0.61–2.46)	0.57
Giant cells (by +1 grade)	2.19 (1.03–4.66)	0.04	2.01 (0.87–4.65)	0.10
Severe ischaemic events				
Covariate				
Age (10yr increments)	2.70 (1.38–5.29)	0.004	2.72 (1.26–5.88)	0.01
Fever	0.19 (0.04–0.87)	0.03	0.29 (0.05–1.82)	0.19
ESR (increments of 10 mm/1 h)	0.86 (0.72–1.01)	0.07	0.86 (0.70–1.06)	0.16
PTL (increments of 10 ⁵ /mm ³)	0.92 (0.69–1.23)	0.57	1.13 (0.75–1.69)	0.56
MPV (fl)	1.70 (0.91–3.20)	0.10	1.32 (0.60–2.91)	0.50
ASA: yes	0.85 (0.30–2.39)	0.76	0.86 (0.25–2.96)	0.81
Intima proliferation (by +1 grade)	1.43 (0.85–2.38)	0.17	1.41 (0.71–2.81)	0.32
Giant cells (by +1 grade)	1.27 (0.77–2.11)	0.35	1.22 (0.62–2.39)	0.57

^aBased on patients with non-missing data of the respective covariate only. ^bAdjusted for all other covariates, based on data from all patients using multiple imputation. PTL: platelet count; Intima: grade of arterial occlusion due to intimal proliferation; giant cells: frequency of giant cells present in biopsy.

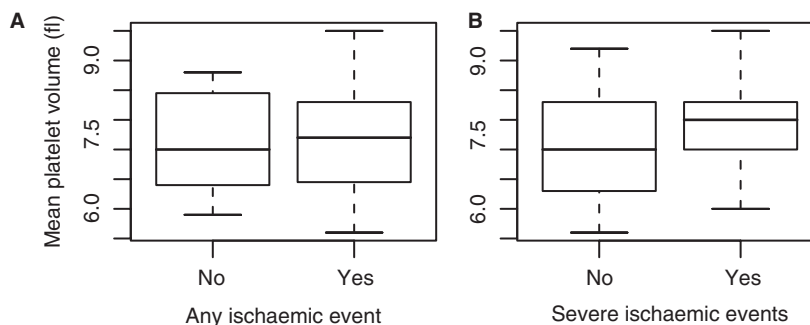


FIG. 1. Box plots of mean platelet volume in patients with GCA grouped according to the occurrence of 'ischaemic events' and 'severe ischaemic events'. The MPV did not significantly differ between GCA patients presenting with or without any ischaemic event (A) or with or without severe ischaemic events (B), respectively.

patients with GCA, which is to our knowledge the largest Swiss GCA cohort reported to date. Patient characteristics were comparable with those reported by others, and accepted risk factors for ischaemic events ['all events'; fever (inverse relation) and 'severe events'; age] were confirmed [2–6]. The high prevalence of permanent visual loss observed in our cohort might relate to the large percentage of patients referred to us from the Department of Ophthalmology [2–6]. Of note, in multiple logistic regression analyses, neither platelet count nor size nor ASA treatment was found to be significantly associated with severe ischaemic events. However, due to the low number of events, CIs were wide and do not exclude clinically relevant effects of these factors.

Previous studies yielded conflicting results regarding the correlation of platelet count, platelet inhibition and ischaemic events [2, 4–7, 11, 18]. In line with our findings, Gonzalez-Gay *et al.* [7]—reporting the largest as yet published GCA cohort ($n=240$)—found no difference in platelet counts of patients with vs those without severe ischaemic events. As for platelet inhibition it is noticeable that in the largest study that linked ASA treatment to protection from ischaemic events [10], the percentage of study participants treated with ASA was much higher than in both the study by Gonzalez-Gay *et al.* and the herein reported cohort. Differing patient populations thus might limit study comparability. While it can, of course, be envisioned that specific subgroups of GCA patients benefit from ASA (stratified, e.g., for co-morbidities, genetic background, etc.) [5, 10], large and prospectively designed cohorts are much needed to provide us with more definite evidence.

The association of specific pathological changes with an increased risk for permanent visual loss is a biological plausibility [8, 9]. Our data fail to directly reproduce this association. However, our finding of a statistical link between 'jaw claudication' and pathological changes, and the fact that 'jaw claudication' *per se* was a predictor of 'severe ischaemic events' (including 'AION'), suggests that methodological rather than biological issues account for this discrepancy. For example, the pool of patients from which a study population is recruited (e.g. ophthalmology referral centre vs internal medicine referral centre) may not only impact the proportion of patients affected by a given ischaemic complication, but also select for study participants with inherently differing risk profiles.

In summary, our study clearly indicates that—with regards to the risk of irreversible ischaemic events in patients newly diagnosed with GCA—clinicians should make no assumptions based on a patient's status with regards to already established platelet inhibition. Prospective studies are urgently needed to thoroughly assess the role of platelet inhibition in patients with GCA.

Rheumatology key messages

- Severe ischaemic events occur with high prevalence despite established platelet inhibition.
- Neither platelet count nor size is strongly associated with the risk of severe ischaemic events.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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