Risk factors for severe cranial ischaemic events in patients with giant cell arteritis

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ABSTRACT

Objective. *Cranial ischaemic events constitute a significant component in the clinical spectrum of giant cell arteritis (GCA). Our aim was to investigate whether cardiovascular risk factors, specific medications and baseline clinical features are associated with the development of severe cranial ischaemic events in GCA patients.*

Methods. *Retrospective analysis of GCA patients. Information collected included baseline clinical and laboratory data, comorbidities, cardiovascular risk factors and medications. GCA Patients with and without severe cranial ischaemic complications were compared.*

Results. *A total of 83 patients with GCA were included in the study. Among them, 24 (29%) patients developed severe cranial ischaemic events. Compared with patients without severe cranial ischaemic events, those with severe cranial ischaemic events had lower erythrocyte sedimentation rate (ESR) levels at diagnosis (81±17 vs. 93±21, p=0.018) and were more likely to have jaw claudication (37.5% vs. 17%, p=0.043). Rate of cardiovascular risk factors and rate of use of anti-platelets and statins were similar between the two groups. The use of β-blockers was higher among patients with severe ischaemic events (46% vs. 20%, p=0.019). Logistic regression analysis showed that lower ESR levels (OR=0.967, 95% CI, 0.94, 0.99) and β-blockers use (OR=4.35, 95% CI, 1.33, 14.2) predicted development of severe cranial ischaemic complications.*

Conclusions *The present study demonstrated that GCA patients with severe cranial ischaemic events had lower inflammatory responses and were more likely to have been treated with β-blockers. Cardiovascular risk factors and antiplatelet therapy had no effect on the occurrence of severe cranial ischaemic events.*

Background

Giant cell arteritis (GCA) is the most common type of vasculitis among people aged more than 50 years (1, 2). The clinical spectrum of GCA is wide and may be classified into two major subsets: symptoms related to cranial arteritis, and symptoms related to extra cranial arteritis. An additional subset is related to the ischaemic manifestations of GCA (3-6). GCA-related severe cranial ischaemic events occur in up to 20–50% of patients and include vision loss and less commonly cerebrovascular accidents (CVA) (7). These events constitute the leading cause of GCA-related morbidity (8-11). Most cranial ischaemic events occur at the presentation of GCA. However, they may develop shortly after corticosteroid initiation or later on, during steroid tapering (12-17). The ischaemic damage in GCA is attributed to occlusive vasculopathy caused by intimal hyperplasia and mediated by several inflammatory mediators, mainly interferon (IFN)-gamma and platelet derived growth factor (PDGF) (18-20). Previous studies have found that jaw claudication and thrombocytosis constitute a risk for severe cranial ischaemic events in GCA. On the other hand, elevated liver enzymes and constitutional syndrome have been found to decrease the risk of severe cranial ischaemic events (12, 21, 22). Several studies have evaluated the influence of traditional cardiovascular (CV) risk factors and the effect of antiplatelet therapy on the development of severe cranial ischaemic events in GCA patients (23-28). The conclusions of these studies are conflicting. Some studies have found that the presence of traditional risk factors of atherosclerosis increased the risk of developing severe cranial ischaemic events (23, 27) while others have not demonstrated any association between the two (24, 28). The effect of antiplatelet therapy on the development of severe cranial ischaemic

complications in GCA is also controversial. Two retrospective studies have shown that antiplatelet therapy may reduce the risk of ischaemic events in patients with GCA (25, 28). Other studies (24, 26, 27) have not confirmed the protective role of antiplatelet therapy in preventing ischaemic events in GCA. There is currently no evidence from randomised control studies determining the safety and efficacy of low-dose aspirin as an adjunctive treatment in GCA (29). In light of the inconclusive data regarding this issue we aimed to assess the effect of clinical and laboratory parameters, as well as cardiovascular risk factors and selected medications, on the development of severe cranial ischaemic events among GCA patients.

Patients and methods

We retrospectively reviewed all patients who were diagnosed with GCA in the Chaim Sheba medical centre between the years 2000 and 2016. Patients' medical records at the time of GCA diagnosis were reviewed. Data collected included clinical and laboratory characteristics, comorbidities, and selected medications.

Clinical and laboratory data

The clinical data collected included the presence of constitutional symptoms, headache, jaw claudication, symptoms compatible with polymyalgia rheumatic (PMR), visual manifestations, cerebrovascular manifestations and an abnormal temporal artery on physical examination. The following laboratory data was collected: haemoglobin, leukocytes and platelets levels, ESR and the presence of elevated liver enzymes. The following medications were selected: antiplatelets (acetylsalicytic acid or clopidogrel), anticoagulants, β-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blocker (ARB), lipid lowering drugs (statins), calcium channel blockers (CCB) and diuretics (furosemide or hydrochlorothiazide). Traditional cardiovascular risk factors recorded included hypertension, diabetes mellitus, hypercholesterolaemia, congestive heart failure, ischaemic heart disease, cerebrovascular accidents and smoking history.

Table I. Baseline clinical and laboratory findings in 83 patients with GCA.

	Variable
Males, no. (%)	28 (34)
Age (years) ± SD (range)	72.5±8.9 (54-90)
Headache, no. (%)	62 (75)
Constitutional syndrome, no. (%)	51 (61)
Abnormal temporal artery biopsy on physical examination, no. (%)	20 (24)
Jaw claudication, no. (%)	19 (23)
Polymyalgia rheumatica, no. (%)	27 (32.5)
Visual manifestations, no. (%)	23 (28)
Cerebrovascular accients, no. (%)	3 (3.6)
Elevated liver enzymes, no. (%)	18 (22)
ESR (mean+SD) mm/1st hour ± SD (range)	89.5±20.1 (50-141)
Haemoglobin (g/Dl) mean ± SD (range)	11.4±1.3 (8.7-15)
Platelet count /mm^3 mean ± SD (range)	397±144 (173-815)
Leukocyte count - cells/microL ± SD (range)	11.2±7.3 (4.4-66.7)
Leukocyte count>11000 cells/microL, no. (%)	30 (36)
Anaemia (haemoglobin <12g/dl), no. (%)	55 (66)
Thrombocytosis (platelets >450 x 10^3/µl), no. (%)	22 (27)
Biopsy proven GCA, no. (%)	59 (71)
Length of temporal artery specimen, cm. ± SD (range)	1.16±0.68 (0.3-3.5)
Temporal artery specimen length <1, cm. (%)	38 (46)

*GCA: Giant cell arteritis.

GCA diagnosis

Diagnosis of biopsy proven GCA required the histological findings of interruption of the internal elastic lamina with infiltration of mononuclear cells into the arterial wall (30). Patients with isolated vasa vasorum vasculitis were excluded from the study. Patients were diagnosed with biopsy-negative GCA based on clinical judgment of the treating physician, provided the patient's symptoms and signs improved within 3 days of corticosteroid treatment (40mg of prednisone or more), no other better alternative diagnosis could be reached after a thorough evaluation and clinical follow-up, and the patient fulfilled the ACR 1990 classification criteria for GCA (31).

Comparison between patients with and without severe cranial ischaemic events

Patients were considered to have severe ischaemic events if they had visual manifestations (transient or permanent visual loss) or CVA (stroke or transient ischaemic attack). Isolated diplopia was not considered a severe ischaemic event. Severe cranial ischaemic events were attributed to GCA if they occurred at diagnosis or up to 4 weeks after initiation of corticosteroids. Clinical and laboratory parameters, comorbidities and selected medication usage were compared between GCA patients with and without severe cranial ischaemic events.

Statistical analysis

Data were analysed with SPSS software v. 23.0. (SPSS Inc. Headquarters, 233 S. Wacker Drive, 11th floor Chicago, Illinois 60606, USA). The significance levels were set at 0.05. Baseline clinical and laboratory findings in patients with GCA are presented as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables.

Comparisons between patients with and without severe cranial ischaemic complications in baseline clinical and laboratory findings, comorbidities and drug therapy at GCA diagnosis were performed by Chi-Square tests for categorical variables and independent *t*-test for continuous variables. Multivariate analysis to predictive variables related to severe cranial ischaemic complications among patients with GCA, was performed by logistic regression models. Odds ratios and 95% confidence Intervals were calculated. The analysis included independent variables/covariates that were statistically significant in the univariate analyses.

Results

During the study period, 83 patients met the inclusion criteria for final analysis. The mean age of the patients was 72.5 (±8.9), and 28 (34%) were males. The most common presenting symptoms were headache (75%), constitutional syndrome (51%) and PMR (27%). A total of 59 patients (71.1%) had a biopsy-proven diagnosis (Table I). Overall, 24 of 83 (29%) patients had one or more severe cranial ischaemic events. Patients with severe cranial ischaemic events had lower ESR levels (81±17 *vs*. 93±21, p=0.018) and a higher rate of jaw claudication in comparison with patients without severe cranial ischaemic events (37.5% *vs*. 17%, p=0.043) (Table II). The rate of atherosclerosis risk factors, CV diseases (ischaemic heart disease, CVA, congestive heart failure) were similar among patients with and without severe cranial ischaemic events. The usage rate of anti-platelets and anticoagulants was similar between patients with and without severe cranial ischaemic events. The usage rate of statins and other selected medications (angiotensin converting enzymes inhibitor, angiotensin receptor blockers, statins, diuretics and calcium channel blockers) was also similar among patients with and without severe cranial ischaemic events. The rate of β-blockers usage was significantly higher among patients with severe cranial ischaemic events compared to those without (46% *vs*. 20%, p<0.05) (Table III). Using multivariate analysis, predictors for severe cranial ischaemic events among patients with GCA were lower ESR levels (OR=0.967, 95% CI, 0.94, 0.99) and β-blocker use (OR=4.35, 95% CI, 1.33, 14.2) (Table IV).

Table II. Baseline clinical and laboratory features of GCA patients: comparative analysis between patients with and without severe cranial ischaemic complications.

Variable	All GCA patients (n=83)	With severe cranial ischaemic complications (n=24)	Without severe cranial ischaemic complications (n=59)	*p*-value
Males, no. (%)	28 (34)	9 (37.5)	19 (32.2)	0.644
Age (years±SD)	72.5 ± 8.9 (54–90)	74 ± 8	72 ± 9	0.308
Headache, no. (%)	62 (75)	18 (75)	44 (75)	0.968
Constitutional syndrome, no. (%)	51 (61)	11 (46)	40 (68)	0.062
Abnormal temporal artery biopsy on physical examination, no. (%)	20 (24)	7 (29)	13 (22)	0.491
Jaw claudication, no. (%)	19 (23)	9 (37.5)	10 (17)	0.043
Polymyalgia rheumatica, no. (%)	27 (32.5)	8 (33)	19 (32)	0.921
Visual manifestations, no. (%)	23 (28)	23 (96)	0	<0.001
Cerebrovascular accients, no. (%)	3 (3.6)	3 (12.5)	0	0.006
Elevated liver enzymes, no. (%)	18 (22)	2 (8.3)	16 (27)	0.060
ESR (mean+SD) mm/1st hour ± SD	89.5 ± 20.1 (50-141)	81 ± 17	93 ± 21	0.018
Haemoglobin (g/Dl) mean ± SD	11.4 ± 1.3 (8.7-15)	11.8 ± 1.4	11.2 ± 1.3	0.052
Platelet count /mm^3 mean ± SD	397 ± 144 (173-815)	387 ± 135	402 ± 148	0.679
Leukocyte count - cells/microL ± SD	11.2 ± 7.3 (4.4–66.7)	11.0 ± 4.0	11.3 ± 8.3	0.817
Anaemia (haemoglobin <12g/dl), no. (%)	55 (66)	15 (62.5)	40 (68)	0.644
Thrombocytosis (platelets >450x10^3/μl), no. (%)	22 (27)	5 (21)	17 (29)	0.431

*GCA: Giant cell arteritis.

Table III. Comorbidities and drug therapy at GCA diagnosis: comparative analysis between patients with and without severe cranial ischaemic complications.

Variable	All GCA patients (n=83)	With severe cranial ischaemic complications (n=24)	Without severe cranial ischaemic complications (n=59)	*p*-value
Comorbidities				
Hypertension	49 (59)	15 (62.5)	34 (58)	0.682
Diabetes mellitus	17 (20.5)	6 (25)	11 (19)	0.515
Hypercholesterolaemia	23 (28)	6 (25)	17 (29)	0.725
Congestive heart failure	2 (2.4)	1 (4.2)	1 (1.7)	0.506
Ischaemic heart disease	7 (8.4)	3 (12.5)	4 (6.8)	0.395
Cerebrovascular accident	5 (6.0)	1 (4.2)	4 (6.8)	0.650
Heavy smoking	10 (12.2)	4 (16.7)	6 (10.3)	0.426
Medications				
Anti-platelets	24 (29)	7 (29)	17 (29)	0.974
Anti-coagulants	4 (4.8)	1 (4.2)	3 (5.1)	0.859
Beta blockers	23 (28)	11 (46)	12 (20)	0.019
ACEI/ARB	29 (35)	7 (29)	22 (37)	0.616
Statins	21 (25)	5 (21)	16 (27)	0.550
Diuretics	15 (18)	4 (17)	11 (19)	0.832
Calcium channel blockers	19 (23)	6 (25)	13 (22)	0.771

*ACE: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Discussion

In our study, we showed that GCA patients with severe cranial ischaemic events had lower inflammatory responses and were more likely to have been treated with β-blockers. Cardiovascular risk factors and antiplatelet therapy had no effect on the occurrence of severe cranial ischaemic events. Severe cranial ischaemic events occur in 20–50% of GCA (7, 8). They mainly include vision loss, and to a lesser extent CVA, and constitute the leading cause of GCA-related morbidity (7-12). Prevention of severe cranial ischaemic events is the main objective in the treatment of GCA. Therefore, investigating risk factors for development of these events imperative. In our study, patients with severe ischaemic events had lower ESR levels in comparison with those without ischaemic events. This finding is consistent with

previous studies that have found that lower inflammatory response is associated with development of severe cranial ischaemic events in GCA (12, 23, 24). Lopez-Diaz *et al*. found that ESR at time of disease diagnosis was associated with the risk of visual ischaemic complications and blindness among in biopsy-proven GCA patients (32). An ESR between 70 and 100mm/1st hour was the best predictor of visual ischaemic complications and permanent visual loss. According to their observation, a moderate degree of inflammation is still required to experience severe ischaemic events in GCA. In a population-based study that encompassed 161 biopsy-proven GCA patients, *amaurosis fugax* was a strong predictor of permanent visual loss in biopsy proven GCA patients (33). In the same population, an extension of the former study that included 240 biopsy-proven GCA patients showed that GCA patients with anaemia had less commonly severe ischaemic events (34). These findings are in acceptance with those of our study, which demonstrated that patients with severe cranial ischaemic events had slightly higher haemoglobin levels (11.8±1.4 *vs*. 11.2±1.3), although the difference did not reach clinical significance. This finding is compatible with the previous finding that GCA patients with cranial ischaemic events have lower inflammatory markers. The inverse correlation between inflammatory response and severe ischaemic events may be explained by the variations in the clinical spectrum of GCA. Weyand *et al*. (18) have previously found a correlation between cytokine messenger RNA (mRNA) expression in affected temporal arteries and different clinical patterns in GCA. Patients with ischaemic symptoms expressed higher concentration of interferon-gamma mRNA and IL-1 beta mRNA, whereas fever was correlated with lower copies of IFN gamma. Tissue from patients with concomitant PMR contained higher levels of IL-2 mRNA transcripts. Genetic factors have also been found to have potential influence on the risk of severe ischaemic events in GCA patients. HLA-DRB1 *04 alleles were associated with disease susceptibility and increased risk of visual ischaemic events (35). In addition, a functional variant (rs2010963) located in the 5' untranslated region of the VEGF gene was associated with severe ischaemic events in biopsy-proven GCA patients referee (36). Moreover, genetic variants associated with high IFN gamma expression were increased in biopsy-proven GCA patients with severe visual ischaemic events, whereas those associated with low IFN gamma expression were more commonly observed in patients with isolated PMR compared to those with biopsy-proven GCA (37). In light of these findings, it is expected that GCA patients presenting clinical symptoms mainly related to cranial arteritis have a lower inflammatory response compared to other patients displaying systemic manifestations. This finding must be taken into account in the clinical workup of patients with cranial ischaemic symptoms, mainly anterior ischaemic optic neuropathy. Among clinicians it is accepted that inflammatory markers are substantially elevated in GCA. In patients with cranial ischaemic symptoms and signs without other features of GCA, inflammatory markers may be only slightly elevated. In these cases, it is crucial to question patients regarding other clinical symptoms related to GCA. Moreover, among patients with cranial ischaemic symptoms suggestive of GCA and normal or slightly elevated inflammatory markers, the diagnosis of GCA should not be disregarded.

Table IV. Multivariate analysis - predictive variables for severe cranial ischaemic complications among patients with GCA.

Variable	OR (95% CI)	*p*-value
Jaw claudication	2.29 (0.68–7.71)	0.180
ESR	0.967 (0.94–0.99)	0.043
Haemoglobin	1.25 (0.78–1.99)	0.356
Beta blockers	4.35 (1.33–14.2)	0.015

Predictors for severe cranial ischaemic complications are: ESR and beta blocker use.

The rate of atherosclerosis risk factors and CV diseases were similar among patients with and without severe ischaemic cranial events. Several studies have evaluated the association between CV diseases and risk factors and ischaemic events in GCA. Data are inconclusive. Salvarani *et al*. (23) have found that hypertension and a past history of ischaemic heart disease are associated with a higher risk of developing severe cranial ischaemic events. Gonzalez-Gay *et al*. (27) have also shown that GCA patients with hypertension exhibited a significantly increased risk of developing severe ischaemic events. Other studies have not found any association between CV risk factors and diseases and the development of severe cranial ischaemic events (24, 28). The ischaemic damage in GCA is attributed to occlusive vasculopathy caused by intimal hyperplasia and mediated by several inflammatory mediators (18-20). It has been suggested that atherosclerosis and the inflammatory process in GCA may interact increasing the risk of ischaemic events (23). This hypothesis could not be discarded. However, the selective ischaemic damage in GCA, mainly affecting the posterior ciliary artery (9), and to a lesser extent other cranial arteries, supports the concept that the ischaemic process in GCA is mainly mediated by inflammation. The effect of antiplatelet therapy on the development of ischaemic events in GCA is also controversial. Two retrospective studies have (25, 28) found that antiplatelet therapy may reduce the risk of ischaemic events in patients with GCA. Based to these studies, it is common practice to prescribe aspirin to patients diagnosed with GCA. In the study conducted by Nesher *et al*. 57 of 175 GCA patients had cranial ischaemic events. Among these, 40 (70%) had vision loss and 17 (30%) had a CVA (25). In this context, it should be noted that stroke is uncommon in GCA. The occurrence of stroke attributed to GCA was reported in only 3% of patients (38). Moreover, documented involvement of intracra-

nial vessels in GCA is rare (39). Accordingly, the rate of stroke in Nesher's study population seems relatively high, and it is possible that not all cases of CVA could be attributed with certainty to GCA. Therefore, the protective role of aspirin solely on cranial ischaemic events attributed to GCA is questionable. In our study, the usage rate of antiplatelets and anti-coagulants was similar between patients with and without severe cranial ischaemic events. This is consistent with several other studies which did not confirm the protective role of aspirin in preventing cranial ischaemic events in GCA patients (24, 26, 27). Use of low dose aspirin, particularly in combination with high-dose corticosteroids in an elderly population, may pose a significant risk (40). In light of the conflicting data regarding the use of aspirin in GCA patients, its use should be considered taking into account the risk-benefit ratio. Further large-scaled prospective studies evaluating this issue are required.

In our study, only 3 patients had strokes. All 3 were diagnosed based on clinical and computerised tomography (CT) findings. One patient had a stroke in the vertebrobasilar artery territory and two had a stroke in the carotid artery territory. Previous studies had demonstrated that vertebrobasilar strokes are more common than carotid ones in GCA patients, and that strokes, especially in the vertebrobasilar territory, are associated with ophthalmic ischaemic events (38, 41). In our study, 2 of the 3 patients with stroke had ophthalmic ischaemic events (one with a vertebrobasilar stroke and one with a stroke in the carotid territory). In light of the small number of patients with stroke in our study, we could not determine any significant association between strokes and ophthalmic ischaemic events. The usage of statins and other selected medications, including angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), diuretics and calcium channel blockers was not associated with development of severe cranial ischaemic events in our study. An interesting finding in our study was the association between β-blocker use and development of severe cranial ischaemic events, which was found significant in the multivariate analysis. This finding was similarly observed in a recent study (24). One possible explanation offered is that β-blockers may increase systemic vascular resistance and thus causing cerebral hypoxia, a phenomenon demonstrated in several animal models (42, 43). The higher usage rate of β-blockers among patients with severe cranial ischaemic events may also indicate a tendency for higher blood pressure levels in this group of patients compared to patients without cranial ischaemic events. Therefore, a possible effect of hypertension on the development of cranial ischaemic events, observed in previous studies (23, 27), may have been masked. The possible effect of β-blockers on the development of severe cranial ischaemic events in GCA and the exact mechanism involved should be further investigated. Our study has several limitations. First, it is a retrospective study. Secondly, we did not have complete data regarding C reactive protein (CRP) levels. Thirdly, the sample size is relatively small. However, patients' clinical and laboratory features were similar to other larger studies (12, 21-28). Therefore, we believe our observations may be generalisable for GCA patients. In conclusion, our study demonstrated that lower ESR levels and β-blocker use are associated with development of severe cranial ischaemic events in GCA patients. In addition, we did not observe any impact of CV risk factors and antiplatelet treatment on the occurrence of severe cranial ischaemic events.

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