Ocular ischaemic complications in giant cell arteritis: $CHADS_2$-score predicts risk of permanent visual impairment

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ABSTRACT

Objective. *To identify independent risk factors for permanent visual loss (PVL) in patients with giant cell arteritis (GCA), with a special focus on sonographic findings of the temporal, carotid and subclavian/axillary arteries, and on established scoring systems of ischaemia risk assessment.*

Methods. *Consecutive patients with a diagnosis of GCA between 2002 and 2013 were retrospectively identified from a prospectively maintained database. Data on clinical characteristics including ophthalmological findings, laboratory values, and sonographic findings of the temporal, carotid an axillary arteries were extracted. $CHADS_2$- and CHA_2DS_2-VASc-score were calculated. Clinical, laboratory and sonographic characteristics of patients with and without PVL were compared. Multiple logistic regression models were calculated to identify variables independently associated with PVL.*

Results. *One-hundred-fifty-two patients were included in the analysis. PVL occurred in 30.2% of patients, with anterior ischaemic optic neuropathy as predominant underlying cause (91.3%). The frequency of PVL was strongly dependent on the age at diagnosis, with a significant increase after the age of 70 years. In multivariate analysis, axillary artery vasculitis with an odds ratio (OR) of 0.3 and constitutional symptoms with an OR of 0.1 were negatively associated with PVL. A $CHADS_2$-score of 1 (OR 10.7) or ≥2 (OR 25) was associated with a significantly increased risk of PVL.*

Conclusion. *The risk of PVL secondary to GCA increases with age but is lower in patients presenting with constitutional symptoms and/or exhibiting axillary artery involvement. The $CHADS_2$-score may help to discriminate patients with low vs. high risk of PVL.*

Introduction

Permanent visual loss (PVL) secondary to optic nerve and/or retinal ischaemia remains the most dreaded early complication of giant cell arteritis (GCA) (1, 2). Most of the previous studies investigating risk factors for PVL relied on patients with biopsy proven cranial GCA (1). However, biopsy-negative GCA carries a significant albeit lower risk of PVL (3). Moreover, the value of temporal artery biopsy as a routine procedure in the diagnostic workup of GCA is doubted today more than ever before (4). In contrast, the role of non-invasive vascular imaging in the diagnosis of GCA has been increasing continuously. Based on imaging studies from the past two decades, GCA nowadays is considered a disease with varying but overlapping disease patterns involving the cranial and/or extracranial arteries (5, 6).

We analysed our cohort of unselected patients with GCA in order to identify clinical risk factors for PVL. Particular emphasis was laid on sonographic findings of the temporal, carotid and subclavian/axillary arteries, and on established scoring systems of ischaemia risk assessment ($CHADS_2$ and CHA_2DS_2-VASc).

Patients and methods

Data collection

Consecutive patients with a diagnosis of GCA between 2002 and 2013 were retrospectively identified from a prospectively maintained database. The diagnosis of GCA was based on a positive temporal artery biopsy, fulfilment of at least three of the 1990 American College of Rheumatology classification criteria for GCA, and/or the presence of typical sonographic findings (Halo) of the temporal and/or axillary arteries, together with a typical clinical and laboratory constellation rapidly responsive to glucocorticoid treatment (6). All

patients with symptoms suggestive of ocular ischaemic complications were routinely evaluated by a board-certified ophthalmologist, including funduscopic examination.

Data on demographic characteristics, clinical symptoms, physical examination, cardiovascular comorbidities, and laboratory findings were extracted from the database. Constitutional symptoms were defined as the presence of fever (including low grade fever >37°) and/or weight loss of at least 4 kg (7). PMR was defined as marked pain and stiffness of the hip and/or shoulder girdle muscles (7). Atrial fibrillation was considered as comorbidity, when already known prior or diagnosed during the inpatient stay leading to a final diagnosis of GCA.

Ophthalmologic examinations were reviewed by an experienced ophthalmologist in order to differentiate arteritic from non-arteritic causes of visual impairment. The following ocular symptoms were evaluated: transient visual loss (*amaurosis fugax*), diplopia, and PVL. PVL was defined as permanent reduction of best-corrected distance visual acuity to less than 20/25 and/or visual field loss of the affected eye(s). Visual symptoms were attributed to GCA when they occurred within 4 weeks prior to diagnosis of GCA and funduscopy showed typical findings of anterior ischaemic optic neuropathy (AION), signs of ischaemic retinopathy such as cotton wool spots, and/or central retinal artery occlusion (CRAO) in one or both eyes.

Patients were categorised with regard to the presence or absence of arteriosclerotic plaques in carotid artery duplex sonography (focal wall thickening of more than 50% compared to the adjacent intima media complex). $CHADS_2$-score and CHA_2DS_2-VASc score were calculated based on the clinical information available at the time of diagnosis (8). Both scores incorporate the following items: congestive heart failure, hypertension, age >75 years, diabetes mellitus, prior stroke/transient ischaemic attack. The CHA_2DS_2-VASc score additionally includes peripheral vascular disease, age 65–74 years, and female sex. Most of the items are scored with one point except stroke (2 points in both scores) and age >75 years (2 points in CHA_2DS_2-VASc).

Table I. Comparison of patients with and without permanent visual loss.

Variable	Patients without permanent visual loss	Patients with permanent visual loss	*p*-value
Age, years (mean ± SD)	67.4 ± 8.1	77.1 ± 7.2	**<0.01**
Female sex (%)	75.5	71.7	0.69
Headache (%)	54.7	50	0.60
Jaw claudication (%)	30.2	50	**<0.01**
Preceding transient visual impairment (%)	13.2	8.7	0.59
Polymyalgia rheumatica (%)	45.3	19.6	**<0.01**
Constitutional symptoms (%)	61	32.6	**<0.01**
Abnormal clinical examination of the temporal arteries (%)	32.7	58.7	**<0.01**
Halo of the temporal arteries halo (%)	46.7	81.8	**<0.01**
Vasculitis of the axillary arteries (%)	57.5	9.3	**<0.01**
History of cardiovascular events (%)	13.2	15.2	0.8
Atherosclerosis of the carotid arteries (%)	64.2	82.6	**0.03**
Atrial fibrillation (%)	8.5	21.7	**0.03**
Arterial hypertension (%)	60.4	82.6	**<0.01**
Diabetes mellitus (%)	16	21.7	0.49
Current smoking (%)	31.4	10.9	**<0.01**
Chronic renal insufficiency (%)	10.4	21.7	0.07
$CHADS_2$-score (mean ± SD)	1.1 ± 1.1	1.9 ± 0.9	**<0.01**
CHA_2DS_2VASc-score (mean ± SD)	2.8 ± 1.5	3.7 ± 1.2	**<0.01**
Anaemia, (%)	59	46.7	0.21
Leucocytosis, (%)	23.8	25	0.60
Thrombocytosis, (%)	25.7	31.1	0.55
ESR, mm / 1 hour (mean ± SD)*	70 ± 36	76 ± 35	0.31
CRP, mg/dl, (mean ± SD)	6.9 ± 6.1	7.9 ± 7.0	0.66
Antithrombotic treatment (%)	22.1	22.7	1.00
Statin treatment (%)	11.5	18.2	0.30

*missing data in 14 patients (9.2%).

Statistical analysis

For univariate analysis, Fisher's exact test and Wilcoxon's rank sum test were applied. Correction for multiple testing was done using the Bonferroni method. To identify independent predictors of PVL, multiple logistic regression models were calculated. Because the parameter "headache" confounded with some variables, this symptom was excluded from the final model. Spearman's rank correlation coefficient was calculated for the ordinal variables of $CHADS_2$- and CHA_2DS_2-VASc2-score. *p*-values less than 0.05 were considered statistically significant.

Results

Cohort characteristics

One-hundred and fifty-two patients were included. *Amaurosis fugax* and/or diplopia were documented in 18 patients, four of whom suffered from PVL at the time of diagnosis. Overall, PVL occurred in 46 patients (30.2%), and 4 patients (9.2%) had bilateral PVL. AION was the predominant cause of PVL (91.3%). CRAO was present in 7 patients, four of whom also exhibited AION of the same or contralateral eye. Table I shows the comparison of clinical characteristics between patients with and without PVL. Ischaemic stroke occurred in two patients.

Clinical predictors of ocular ischaemic complications

Patients with PVL significantly more frequently reported jaw claudication (50% *vs*. 30.2%, $p<0.01$) and exhibited clinical signs (58.7 *vs*. 32.7%, $p<0.01$) and sonographic findings (81.8 *vs*. 46.7%; $p<0.01$) of temporal artery involvement. Moreover, these patients more frequently had arterial hypertension, atrial fibrillation, renal insufficiency, and sonographic evidence of carotid arteriosclerosis (all $p<0.05$, see Table I). By contrast, those without PVL had a higher frequency of polymyalgia rheumatica, constitutional symptoms and extracranial arterial involve-

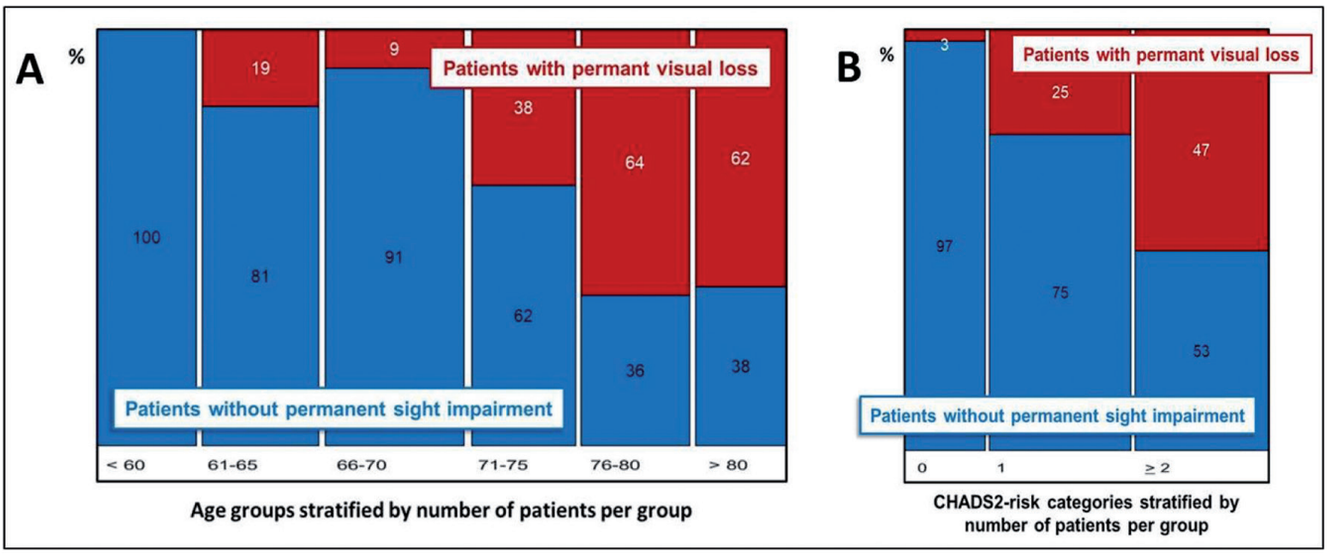

Fig. 1. Mosaic plots showing (**A**) the relative frequency of permanent visual loss in different age groups, and (**B**) the relative frequency of permanent visual loss in different $CHADS_2$-score risk categories.

ment by CDS (all $p<0.05$, see Table I). Noteworthy, fever was not reported in any patient with PVL but was present in 21.7% of patients in the subgroup of patients without PVL ($p<0.01$).

Influence of age and risk stratification with $CHADS_2$-score

The occurrence of PVL was strongly dependent on the age of diagnosis, with a significant increase after the age of 70 (Fig. 1A). $CHADS_2$-score and CHA_2DS_2-VASc-score were highly correlated (Spearman's rho 0.85); therefore the more simple to calculate $CHADS_2$-score was used for further analysis. Figure 1B shows the prevalence of PVL in different risk-categories of the $CHADS_2$-score.

Multiple logistic regression calculations finally revealed a model including clinical variables (constitutional symptoms, $CHADS_2$-score of 1 or ≥2), laboratory values (thrombocytosis) and sonographic findings (vasculitic axillary artery involvement, carotid artery arteriosclerosis). While constitutional symptoms (OR 0.1) and axillary artery vasculitis by CDS (OR 0.3) significantly reduced the likelihood of PVL, $CHADS_2$-categories of 1 (OR 10.7) or higher (OR 25) were independent predictors of PVL (Fig. 2). The remaining variables also increased the probability of PVL, but either without (carotid arteriosclerosis) or only borderline (thrombocytosis) statistical significance.

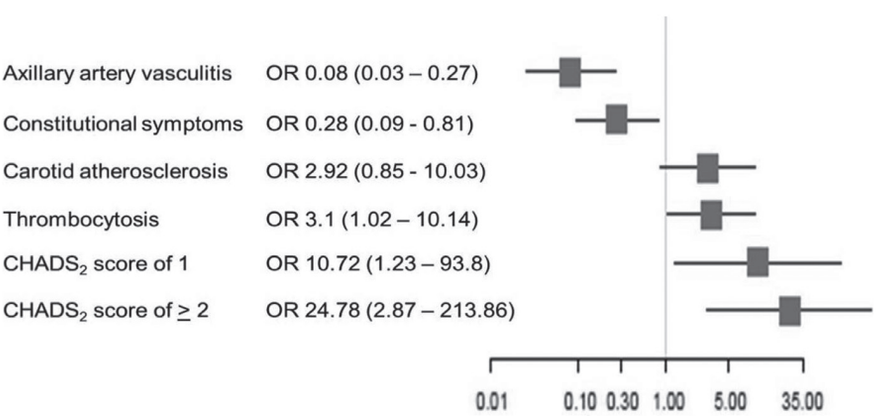

Fig. 2. Forest plot showing the odds ratios with corresponding 95% confidence intervals of the variables included in the final logistic regression model.

Discussion

In our retrospective study of 152 patients with GCA we found that an established ischaemia risk scoring system ($CHADS_2$) had a promising discriminatory value to identify those patients with GCA at low (score=0), intermediate (score =1) and high (score >2) risk of PVL. While largely used in decision making regarding anticoagulation of atrial fibrillation in order to prevent ischaemic stroke (6), few studies showed a correlation between $CHADS_2$-score or CHA_2DS_2-VASc-score and ischaemic events in other clinical settings, such as major cardiac surgery, coronary artery disease and peripheral arterial disease (9-11). Some components of $CHADS_2$, namely older age, arterial hypertension, and cardiac disease by means of ischaemic heart disease, are well known risk factors for cranial ischaemic complications in GCA (7, 12). Pre-existing chronic vascular damage related to increasing age and common cardiovascular risk factors may predispose to occlusion of the small branches of the ophthalmic artery when myointimal hyperplasia secondary to GCA occurs. In line with this hypothesis, we found that carotid artery arteriosclerosis was more common in patients with PVL. A recent analysis of the large Diagnosis and Classification Criteria in Vasculitis Study (DCVAS) cohort identified a history of stroke and peripheral arterial

disease as risk factors for PVL in patients with GCA (13). Finally, Muratore *et al*. demonstrated an association between calcifications in temporal artery biopsy specimens and the occurrence of PVL (14). Atrial fibrillation has not been investigated previously as a possible risk factor for cranial ischaemic events in GCA, but was not an independent predictor of PVL in our study.

Thrombocytosis was an independent predictor of PVL in our cohort. Earlier studies also identified thrombocytosis as predictor of cranial ischaemic events, whereas more recent studies with larger sample sizes did not (7). Nonetheless, this variable adds another potential mechanism to the process finally resulting in vessel occlusion, namely local thrombosis on top of luminal stenosis and/or endothelial dysfunction. Acute thrombosis has been found in 9% of temporal artery biopsy specimens in an Italian study (14), but was not independently associated with ischaemic eye complications in a French series (15). The actual role of local thrombosis for development of ocular ischaemia in GCA has to be determined yet.

We observed a significantly lower risk of PVL in patients presenting with constitutional symptoms at the time of diagnosis. It is remarkable that none of the patients with fever developed ocular ischaemic complications in our study. Constitutional symptoms, and particularly fever, result from an interleukin-6-driven pathway. By contrast, interleukin-6 does not play a dominant role in the development of myointimal hyperplasia which is rather driven by the interleukin-12/interferon-γ-axis. In fact, interleukin-6 has been shown to exhibit angiogenic properties, possibly playing a role in compensating ischaemia (16). As a result, a marked humoral inflammatory response is associated with a considerably lower risk of developing PVL (17). Constitutional symptoms may reflect a disease pattern with predominant extracranial involvement, known to carry a lower risk of ocular ischaemic complications. Schmidt *et al*. showed that axillary artery vasculitis, as depicted by CDS, goes along with a low frequency of visual loss (12). In our study, we confirmed that the sonographic finding of axillary artery vasculitis is an independent negative predictor of ocular ischaemic complications in GCA.

But how could our findings impact clinical practice, given that PVL has already occurred in the majority of patients when the diagnostic workup for suspected GCA is initiated? Risk stratification based on clinical (absence of typical cranial symptoms, presence of constitutional symptoms, $CHADS_2$-score of 0) could identify those subjects at very low risk of developing PVL who may safely undergo the diagnostic workup without empiric glucocorticoid treatment. Whether there is any benefit of immediate intravenous glucocorticoid pulse therapy and/or antithrombotic therapy in order to avoid severe ischaemic complications in patients without PVL at the initial presentation, but stratified as high risk (typical cranial symptoms, $CHADS_2$-score ≥2, thrombocytosis), remains to be investigated.

Despite the limitations of retrospective data collection within a long time frame and wide confidence intervals due to limited sample size, we identified novel (axillary artery vasculitis, $CHADS_2$-score ≥1) and confirmed previously established (constitutional symptoms, thrombocytosis) independent predictive factors of PVL in GCA.

References

1. SORIANO A, MURATORE F, PIPITONE N *et al*.: Visual loss and other cranial ischaemic complications in giant cell arteritis. *Nat Rev Rheumatol* 2017; 13: 476-84.
2. ELEFANTE E, BOND M, MONTI S *et al*.: One year in review 2018: systemic vasculitis. *Clin Exp Rheumatol* 2018; 36 (Suppl. 111): S12-32.
3. GONZALEZ-GAY MA, GARCIA-PORRUA C, LLORCA J *et al*.: Biopsy-negative giant cell arteritis: clinical spectrum and predictive factors for positive temporal artery biopsy. *Semin Arthritis Rheum* 2001; 30: 249-56.
4. LUQMANI R, LEE E, SINGH S *et al*.: The Role of Ultrasound Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis (TABUL): a diagnostic accuracy and cost-effectiveness study. *Health Technol Assess* 2016; 20: 1-238.
5. MONTI S, FLORIS A, PONTE CB *et al*.: The proposed role of ultrasound in the management of giant cell arteritis in routine clinical practice. *Rheumatology* (Oxford) 2018; 57: 112-9.
6. DEJACO C, RAMIRO S, DUFTNER C *et al*.: EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis* 2018; 77: 636-643.
7. SALVARANI C, DELLA BELLA C, CIMINO L *et al*.: Risk factors for severe cranial ischaemic events in an Italian population-based cohort of patients with giant cell arteritis. *Rheumatology* (Oxford) 2009; 48: 250-3.
8. CAMM AJ, LIP GY, DE CATERINA R *et al*.: 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012; 33: 2719-47.
9. ZHOU X, CAO K, KOU S *et al*.: Usefulness of CHADS2 score for prognostic stratification of patients with coronary artery disease: A systematic review and meta-analysis of cohort studies. *Int J Cardiol* 2017; 228: 906-911.
10. HORNERO F, MARTIN E, PAREDES F *et al*.: Stroke after coronary artery bypass grafting: preoperative predictive accuracies of CHADS2 and CHA2DS2VASc stroke risk stratification schemes. *J Thorac Cardiovasc Surg* 2012; 144: 1428-35.
11. GARY T, BELAJ K, HAFNER F *et al*.: A high CHA(2)DS(2)-VASc score is associated with a high risk for critical limb ischemia in peripheral arterial occlusive disease patients. *Atherosclerosis* 2012; 225: 517-20.
12. SCHMIDT WA, KRAUSE A, SCHICKE B *et al*.: Do temporal artery duplex ultrasound findings correlate with ophthalmic complications in giant cell arteritis? *Rheumatology* (Oxford) 2009; 48: 383-5.
13. YATES M, MACGREGOR AJ, ROBSON J *et al*.: The association of vascular risk factors with visual loss in giant cell arteritis. *Rheumatology* (Oxford) 2017; 56: 524-8.
14. MURATORE F, BOIARDI L, CAVAZZA A *et al*.: Correlations between histopathological findings and clinical manifestations in biopsy-proven giant cell arteritis. *J Autoimmun* 2016; 69: 94-101.
15. CHATELAIN D, DUHAUT P, SCHMIDT J *et al*.: Pathological features of temporal arteries in patients with giant cell arteritis presenting with permanent visual loss. *Ann Rheum Dis* 2009; 68: 84-8.
16. HERNÁNDEZ-RODRÍGUEZ J, SEGARRA M, VILARDELL C *et al*.: Elevated production of interleukin-6 is associated with a lower incidence of disease-related ischemic events in patients with giant-cell arteritis: angiogenic activity of interleukin-6 as a potential protective mechanism. *Circulation* 2003; 107: 2428-34.
17. CID MC, FONT C, ORISTRELL J *et al*.: Association between strong inflammatory response and low risk of developing visual loss and other cranial ischemic complications in giant cell (temporal) arteritis. *Arthritis Rheum* 1998; 41: 26-32.