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ORIGINAL RESEARCH

Long delay from symptom onset to first consultation contributes to permanent vision loss in patients with giant cell arteritis: a cohort study

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ABSTRACT

Objectives To characterise factors associated with permanent vision loss (PVL) and potential reasons for the therapeutic delay contributing to PVL in giant cell arteritis (GCA).

Methods Retrospective analysis of GCA patients diagnosed at the University Hospital Basel between December 2006 and May 2021.

Results Of 282 patients with GCA (64% females), 49 (17.4%) experienced PVL. In 43/49 (87.8%) PVL occurred before treatment. Of these, 24 (55.8%) patients had first non-ocular symptoms and eventually sought consultation when PVL occurred in a median of 21 (IQR 14.75–31.0) days after the first symptoms. Only five of the 24 patients had consulted a physician before PVL, but GCA diagnosis was missed. Treatment was initiated rapidly after diagnosis (median 1 day (IQR 0.0–7.0)). PVL on therapy occurred in six patients in a median of 40 (IQR 20.5–67.3) days after treatment started. In two of those, glucocorticoids were tapered too quickly.
In multivariable analysis, patients with PVL were older (OR 1.17, 95% CI 1.07 to 1.29, p=0.001) and reported more frequently jaw claudication (OR 3.52, 95% CI 1.02 to 13.16, p=0.051). PVL was present in 18 (42.9%) of the 42 patients with vasculitic ultrasound findings in all six temporal artery segments. The incidence of PVL over 15 years did not decline (Spearman rank=0.3, p=0.68).

Conclusion The prevalence of GCA-associated PVL remains high. Associated factors were advanced age, jaw claudication and ultrasound findings consistent with vasculitis in all six temporal artery segments. Despite preceding non-ocular GCA symptoms weeks before the onset of PVL, most patients were not seen by a rheumatologist before PVL occurred.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Permanent vision loss (PVL) is a feared complication of giant cell arteritis (GCA). Since the introduction of glucocorticoid treatment and fast-track clinics, the incidence of PVL has decreased but remains at 10%–20%.

WHAT THIS STUDY ADDS

⇒ More than half of the patients experience GCA-related symptoms several weeks prior to the onset of PVL, but most do not seek medical advice until ocular symptoms occur.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The still insufficient awareness of the symptoms, consequences and treatment of GCA among care providers contributes to vision loss.
⇒ Teaching of medical professionals and public education are needed to shorten diagnostic delays and thereby reduce the incidence of PVL in GCA patients.

INTRODUCTION

The clinical presentation of giant cell arteritis (GCA) is heterogeneous and includes constitutional and ischaemic symptoms.[1] The most severe complication remains permanent vision loss (PVL), mainly caused by anterior ischaemic optic neuropathy (AION) involving the posterior ciliary arteries or central retinal artery occlusion (CRAO).[2] Less often, blindness results from posterior ischaemic optic neuropathy (PION) or occipital lobe infarction.[3] Before the advent of glucocorticoid therapy for GCA, PVL occurred in 40%–48%[4–7] of cases and decreased to 10%–20% during the last decades,[8–14] due to an increased awareness of GCA-associated complications and the accepted practice among general practitioners (GPs) to immediately start systemic glucocorticoids in case of suspected GCA.[15] If left untreated, the risk for bilateral AION is high.[16] Transient visual symptoms, age and lower blood levels of inflammatory markers are risk factors for impending vision loss.[4 8 12 13 17–19] In contrast,

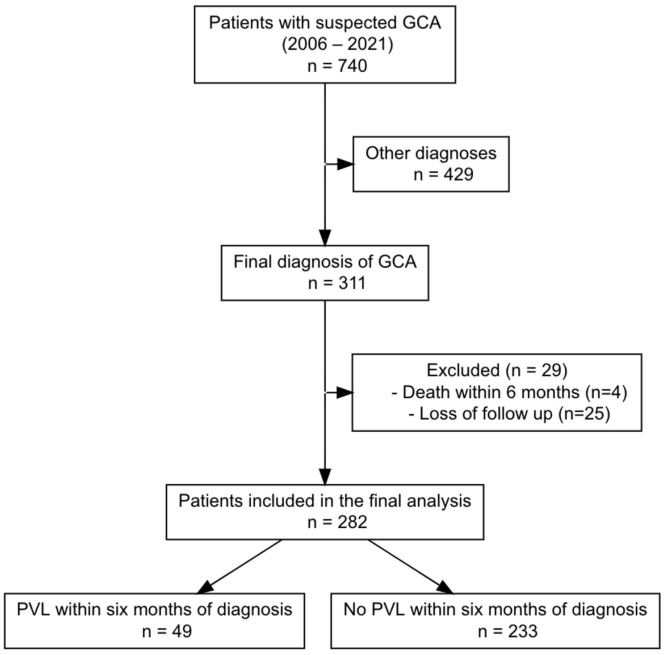

Figure 1 Flow chart of the study population. The initial cohort consisted of patients suspected of having giant cell arteritis (GCA) who underwent colour duplex sonography at presentation. Of these, 282 patients with a final diagnosis of GCA were included in the final analysis.

polymyalgia and constitutional symptoms are associated with a reduced risk for PVL.[4 11 13 18 20] In histopathological studies, PVL has been inconsistently associated with the presence of giant cells and higher intimal hyperplasia scores in temporal artery biopsy.[21–24] Similarly, the detection of temporal arteritis by ultrasound has been associated with ocular ischaemia in some studies.[25 26]

Early diagnosis of GCA and immediate administration of glucocorticoids are essential to effectively prevent PVL, as most ocular ischaemic events occur before treatment.[8] However, once vision loss has occurred, it is usually permanent, and glucocorticoids are administered to preserve the remaining vision.[4 27] The introduction of fast-track clinics, including ultrasound as a first-line diagnostic tool for early GCA diagnosis, intended to reduce the incidence of PVL even further compared with conventional clinical practice.[28–30] In a recent study, a fast-track approach reduced PVL incidence by about 50%, but still, 12.7% experienced PVL.[28] Obviously, patients can only be referred to fast-track clinics (1) if they consult their GPs for GCA-associated symptoms and (2) if their primary care physician suspects them of having GCA. The unspecific character of many GCA-associated symptoms may prevent patients from consulting with their GPs and result in misdiagnoses. A recent systematic review and meta-analysis reported a mean diagnostic delay between symptom onset and GCA diagnosis of 9 weeks.[31] This study aimed to investigate the incidence and risk factors of PVL among patients with GCA treated at our centre during the last 15 years and to identify obstacles in the patient's pathway that may cause a delay in treatment initiation.

METHODS

Patients and setting

We performed a monocentric retrospective analysis of a cohort of patients referred to our clinic with suspected GCA. We routinely perform ultrasound examinations on all patients with suspicion of having GCA. Therefore, for case identification, we analysed all patients who had undergone ultrasound examination for diagnostic workup of suspected GCA at the University Hospital Basel between December 2006 and May 2021. Of those, we included only patients with a final diagnosis of GCA and a follow-up period of at least 6 months after diagnosis. GCA was diagnosed if temporal artery biopsy was positive, if the 1990 criteria from the American College of Rheumatology (ACR) were fulfilled, or if at least 2/5 ACR criteria were fulfilled in combination with typical vasculitic findings in ultrasound, positron emission tomography with CT or MRI.[32]

Data collection

The following data were collected from the local Basel GCA cohort (BARK)[33] and retrospective chart review: patients' demographics, clinical manifestations, the chronology of symptoms, laboratory and imaging findings at the time of GCA diagnosis, results of ophthalmological assessment, place and date of the first consultation, the reason for medical evaluation, date of diagnosis and date of glucocorticoid treatment initiation.

We defined visual impairment as vision loss, visual field loss, blurred vision, diplopia or amaurosis fugax associated with GCA. Transient visual impairment was defined as a temporary ocular symptom that resolved completely within 6 months of diagnosis. PVL was defined as complete vision loss or permanent visual field defect in at least one eye persisting 6 months after GCA diagnosis and occurring within 6 months after diagnosis. Consultation delay is defined as the time interval from GCA-attributable symptom onset to the first consultation with a health professional,[31] and treatment delay as the time between the first consultation for GCA-related symptoms and initiation of glucocorticoid treatment.

Ultrasound

For ultrasound examinations, iU22 ultrasound devices with a linear 9–3 MHz and 17–5 MHz transducer or EPIQ 7 duplex devices with a linear 12–3 MHz and 18–5 MHz transducer (both from Philips, Best, The Netherlands) were used.[34] An experienced angiologist (MA) reread and verified all ultrasound image classifications within the cohort. The following arterial segments were bilaterally categorised as 'normal', 'vasculitis' or 'arteriosclerosis': the common, internal and external carotid arteries, subclavian and axillary arteries, and the superficial temporal arteries (trunk, parietal and frontal branch). 'Vasculitis' in the temporal artery was detected

Table 1 Patient characteristics at the time of diagnosis

Characteristics	All	PVL	No PVL	P value
No of patients, n (%)	282	49 (17.4)	233 (82.6)	–
Age, mean (±SD)	72.9 (±8.3)	77.8 (±7.5)	71.8 (±8.2)	<0.01
Female, n (%)	180 (63.8)	27 (55.1)	153 (65.7)	0.16
BMI, mean (±SD)	25.1 (±5.0)	24.3 (±4.7)	25.3 (±5.1)	0.64
History of PMR, n (%)	44 (15.6)	7 (14.3)	37 (15.9)	0.73
Hypertension, n (%)	143 (50.7)	31 (63.3)	112 (48.1)	0.05
Diabetes mellitus, n (%)	53 (18.8)	16 (32.7)	37 (15.9)	0.006
Dyslipidaemia, n (%)	71 (25.2)	16 (32.7)	55 (23.6)	0.09
Smoking, n (%)	94 (33.3)	15 (30.6)	79 (33.9)	0.72
Coronary artery disease, n (%)	40 (14.2)	7 (14.3)	33 (14.2)	0.99
Cerebrovascular disease, n (%)	35 (12.4)	5 (10.2)	30 (12.9)	0.59
Peripheral artery disease, n (%)	25 (8.9)	7 (14.3)	18 (7.7)	0.17
ESR (mm/h), median (IQR)	70 (40–89)	70 (54–80)	72 (40.0–90.0)	0.75
CRP (mg/dl), median (IQR)	56.9 (27.20–108.8)	44.4 (27.7–90.6)	60.9 (27.3–110.5)	0.26
Leucocytes (G/l), median (IQR)	9.9 (8.1–11.7)	10.13 (8.4–11.7)	9.77 (7.9–11.8)	0.34
Thrombocytes (G/l), median (IQR)	381 (305.0–485.2)	384 (280.0–468.0)	380 (315.0–493.5)	0.49
Haemoglobin (g/l), mean (±SD)	122.0 (±15.6)	121.2 (±17.7)	122.1 (±15.2)	0.73
Fever, n (%)	38 (13.5)	3 (6.1)	35 (15.0)	0.09
Headache, n (%)	169 (59.9)	27 (55.1)	142 (60.9)	0.54
Jaw claudication, n (%)	107 (37.9)	25 (51.0)	82 (35.2)	0.05
Scalp tenderness, n (%)	97 (34.4)	15 (30.6)	82 (35.2)	0.75
Weight loss, n (%)	105 (37.2)	18 (36.7)	87 (37.3)	0.82
Polymyalgic symptoms, n (%)	107 (37.9)	11 (22.4)	95 (40.8)	0.03
Tenderness of the TA, n (%)	83 (29.4)	18 (36.7)	65 (27.9)	0.16

BMI, body mass index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; n, number; PMR, Polymyalgia rheumatica; PVL, permanent vision loss; TA, temporal artery.

using the compression sign.[35] For larger vessels, 'vasculitis' was defined as previously described.[33]

By analogy to the halo count,[26] we calculated the number of affected (ie, 'vasculitis') temporal artery segments (trunk, parietal and frontal branches) on both sides, resulting in a maximum count of six. Patients with missing data in one or more temporal artery segments (e.g., due to temporal artery biopsy in this segment) were excluded from this analysis.

We separately calculated the number of vasculitis-affected segments for the carotid (common, internal and external carotid arteries) and the subclavian/axillary arteries (online supplemental tables S1 and S2).

Statistical analysis

Continuous variables are presented as means with SD or medians with IQRs. Categorical variables are expressed as numbers with percentages. Baseline characteristics of patients who developed PVL within 6 months after diagnosis were compared with the rest of the cohort using the Student's t-test for data with parametric distributions. Data with non-parametric distributions were compared using the Mann-Whitney U test. Categorical variables were compared using the χ^2 test or Fisher's exact test as appropriate. Logistic regression analysis was applied to investigate the association between patient characteristics and PVL at 6 months after diagnosis, reported as ORs with their 95% CIs. Spearman's rank correlation was used to analyse the trend in the incidence of PVL.[36] All statistical analyses were performed in RStudio V.2021.9.0.351 (2021-09-20).

RESULTS

Study cohort

From December 2006 to May 2021, 740 patients with suspected GCA were screened by ultrasound at our centre. GCA was diagnosed in 311 (42%) patients. Of those, 29 were excluded from the study because of missing follow-up (four patients died within 1 month after GCA diagnosis, and 25 patients were lost to follow-up) (figure 1). In total, 282 patients (64% women) with a mean age of 72.9±8.3 years were included in the final analysis (table 1).

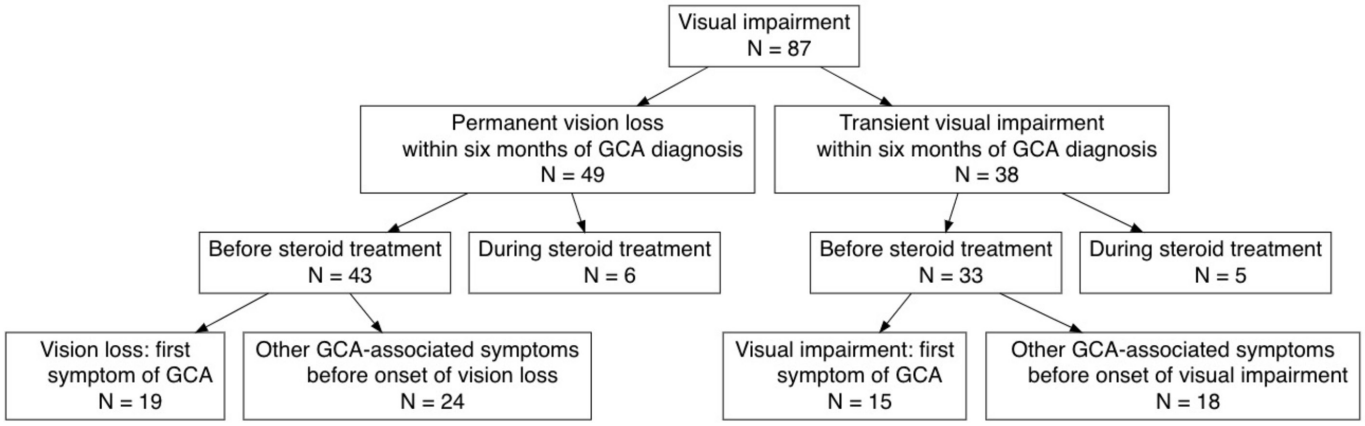

Figure 2 Patients with giant cell arteritis (GCA) and visual impairment (permanent and transient). Half of all patients had GCA-related symptoms before onset of visual impairment.

Visual impairment and trend in the incidence of PVL

Transient and permanent visual impairment associated with GCA were recorded for 87 of 282 patients (30.9%) (figure 2). In 38 (13.5%) patients with transient visual impairment, the most frequent symptoms were diplopia in 22 patients (57.9%) and blurred vision in 10 patients (26.3%). Abducens palsy was the most common diagnosis in 11/38 patients (28.9%). In 20 (52.6%) patients with transient visual impairment, fundus examination did not reveal any pathological findings (table 2). Two patients suffered from transient visual field loss, which resolved completely.

PVL occurred in 49/282 (17.4%) patients. Of these, 15/49 (30.6%) patients presented with complete blindness in at least one eye and 34/49 (69.4%) patients had permanent visual field loss. In 43/49 (87.8%) patients, PVL developed before therapy initiation, and the remaining 6 (12.2%) developed PVL with a median of 40.0 days (IQR 20.5–67.25) after treatment initiation. None of these six patients had visual symptoms at the initiation of treatment. Four of these patients were started on an initial dose of 40–60 mg of prednisone per day with a target dose of 15–20 mg/day within two to 3 months (patients 44, 45, 48, 49, online supplemental table S3).

Table 2 Ocular symptoms and diagnoses of patients with visual impairment

Symptoms*	All (n=87)	PVL (n=49)	TVI (n=38)	P value
Vision loss, n (%)	24 (27.6)	24 (49.0)	0 (0.0)	<0.001
Diplopia, n (%)	23 (26.4)	1 (2.0)	22 (57.9)	<0.001
Visual field loss, n (%)	22 (25.3)	20 (40.8)	2 (5.3)	<0.001
Blurred vision, n (%)	19 (21.8)	9 (18.4)	10 (26.3)	0.37
Amaurosis fugax, n (%)	9 (10.3)	2 (4.1)	7 (18.4)	0.04
Diagnoses	All (n=87)	PVL (n=49)	TVI (n=38)	p-value
AION, n (%)	37 (42.5)	36 (73.5)	1 (2.6)	<0.001
Abducens palsy, n (%)	11 (12.6)	0 (0.0)	11 (28.9)	<0.001
CRAO, n (%)	8 (9.2)	8 (16.3)	0 (0.0)	0.009
CVI, n (%)	5 (5.7)	1 (2.0)	4 (10.5)	0.16
INOP, n (%)	1 (1.1)	0 (0.0)	1 (2.6)	0.44
Normal findings in the examination, n (%)	20 (23.0)	0 (0.0)	20 (52.6)	<0.001
PION, n (%)	1 (1.1)	1 (2.0)	0 (0.0)	1
No examination, n (%)	1 (1.1)	1 (2.0)	0 (0.0)	1
AION+CRAO, n (%)	1 (1.1)	1 (2.0)	0 (0.0)	1
AION+CVI, n (%)	1 (1.1)	0 (0.0)	1 (2.6)	0.44
AION+abducens palsy, n (%)	1 (1.1)	1 (2.0)	0 (0.0)	1

*Some patients had more than one symptom.
AION, anterior ischaemic optic neuropathy; CRAO, central retinal artery occlusion; CVI, cerebrovascular insult; INOP, internuclear ophthalmoplegia; n, number; PION, posterior ischaemic optic neuropathy; PVL, permanent vision loss; TVI, transient visual impairment.

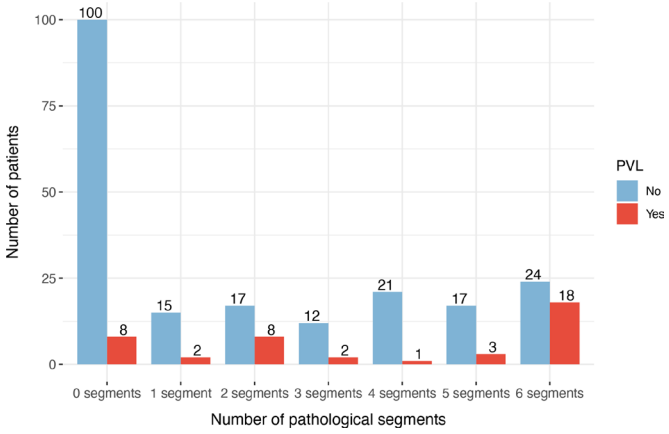

Figure 3 Number of segments with colour duplex ultrasound defined vasculitis in the temporal arteries (trunk, parietal and frontal branches on both sides) in patients with permanent vision loss (PVL) compared with patients without PVL.

However, in two patients treated by their primary care physicians, prednisone was tapered very rapidly before vision loss occurred (patients 46 and 47; online supplemental table S3). The most common cause of PVL was AION in 36 of 49 patients (73.5%) followed by central CRAO in 8 of 49 patients (16.3%).

The proportion of patients who developed PVL has remained constant over the years (Spearman's rank correlation coefficient=0.3, p=0.68), although the number of cases evaluated for suspected GCA progressively increased, as did the number of patients diagnosed with GCA. From 2006 to 2013, 104 patients were diagnosed with GCA, of whom 17 (16.3%) experienced PVL. From 2014 to 2021, 178 patients were diagnosed with GCA, among whom PVL occurred in 32 patients (18.0%) (online supplemental figure S1).

Findings associated with PVL

Patients with PVL were, on average, 6 years older (p<0.01), and more often reported jaw claudication (51.0% vs 35.2%, p=0.05) compared with those without PVL. Polymyalgia was less frequent in patients with PVL than in those without PVL (22.4% vs 40.8%, p=0.03). Furthermore, patients with PVL were more likely to have comorbidities such as diabetes (32.7% vs 15.9%, p=0.006) and hypertension (63.3% vs 48.1%, p=0.05) (table 1). Following multiple logistic regression, the variables age (OR 1.17, 95% CI 1.07 to 1.29, p=0.001) and presence of jaw claudication (OR 3.52, 95% CI 1.02 to 13.16, p=0.051) continued to be associated with PVL.

Colour duplex ultrasound findings

Of our cohort of 282 patients with GCA, a complete set of ultrasound images of all temporal artery segments was available for 248 patients (87.9%), including 42 patients with and 206 without PVL. In patients with PVL, a median of 4.5/6 temporal artery segments (IQR 2.0–6.0) showed vasculitic findings in ultrasound compared with a median of 1/6 temporal artery segments (IQR 0.0–4.0) in patients without PVL (p<0.001). The incidence of PVL was highest when all six temporal artery segments were affected; of 42 patients with vasculitis in all segments, 18 (42.9%) presented with PVL. Of note, 8/42 patients (19.0%) without ultrasound findings in the temporal artery segments presented with PVL (figure 3). We also investigated the association between ocular ischaemia and vasculitis-affected segment counts for the carotid/subclavian/axillary arteries. The number of extratemporal affected segments did not differ between patients with PVL and patients without PVL (online supplemental tables S1 and S2).

Chronology of GCA manifestations, consultation and treatment delay in patients with PVL

In 19 of the 43 (44.2%) patients presenting with PVL before glucocorticoid initiation, vision loss was the first symptom of GCA (online supplemental table S4, cases 1–19). In the remaining 24/43 patients (55.8%), ischaemic or constitutional symptoms had preceded the onset of PVL (online supplemental table S4, cases 20–43).

Consultation delay was shorter in patients who reported vision loss as their first symptom (median 2.0 days after symptom onset, IQR 1.0–3.0 days) than patients with preceding non-ocular GCA-related symptoms (median 21 days after symptom onset, IQR 14.75–31.0 days). Of the latter, the majority consulted a physician only once they suffered visual impairment (online supplemental table S4, case 20–38). Five subjects had consulted a physician before PVL, but the diagnosis of GCA was not considered at that time and no glucocorticoid treatment was initiated until PVL developed later on (online supplemental table S4, case 39–43). Detailed case descriptions of these five patients are found in online supplemental material. The remaining patients who did not develop PVL (n=233) consulted a physician a median of 12 days (IQR 6.0–25.0) after symptom onset, which is significantly faster compared with the 24 patients with PVL and preceding GCA-related symptoms (p=0.005).

Treatment for patients reporting visual impairment started on the same day as the first medical contact (median 0.0 days, IQR 0.0–3.5). In patients without visual impairment, treatment was initiated a median of 2 days after first medical contact (IQR 0.0–8.0).

DISCUSSION

More than 17% of all 282 patients with GCA experienced either partial (12.1%) or complete (5.3%) PVL within 6 months of diagnosis, which is within the range of previously published studies.[8–14] The incidence of PVL over the studied period spanning 16 years remained stable. Although symptoms of GCA were present for weeks in a large proportion of patients, most patients sought medical care only after vision loss had occurred. Treatment was started immediately once the diagnosis of GCA was made. Six patients developed PVL despite established glucocorticoid therapy. This is in line with a recent

study reporting the incidence of new PVL after initiation of glucocorticoid therapy to be 2.2%.[37] Consistent with previous studies, AION was the most common cause of PVL.[3 8]

After multivariable analysis, we could confirm older age[8 38] and jaw claudication as risk factors for PVL.[9 38 39] Conflicting results have been described concerning the association of inflammatory markers with the occurrence of PVL. We found no significant difference in CRP and ESR values between patients with and without PVL, which corroborates data from previous studies.[13 38 39] Others suggested that a strong acute-phase response identifies patients at low risk of PVL,[17] and that a normal ESR is a risk factor for PVL.[8]

The vasculitis-affected segment count of the temporal arteries by ultrasound was significantly higher in patients with PVL than in those without PVL. Most strikingly, when all six temporal artery segments were affected by vasculitis, the prevalence of PVL was 42.9%. However, almost one out of five patients with PVL had a negative ultrasound of the temporal arteries. Thus, treatment should not be delayed in ultrasound-negative patients.

van der Geest *et al* also showed that the extent of ultrasound-defined vascular inflammation of the temporal and axillary arteries is linked to ocular ischaemia in patients with GCA.[26] One previous study by Schmidt *et al* did not find any association between ultrasound findings and the occurrence of ocular ischaemia.[25] However, the definition of ocular ischaemia in the study of Schmidt *et al* was broader and included transient symptoms such as diplopia and amaurosis fugax which might explain some discrepancies. Patients with 6/6 temporal artery segments showing vasculitis in ultrasound may be at risk for imminent vision loss and immediate, intense treatment is suggested.

The PVL incidence of 17.4% in our cohort was similar to that reported by González-Gay *et al* (14.9%),[11] Cid *et al* (14.0%)[17] or Salvarani *et al* (19.1%).[8] In contrast to previously described fast-track clinic approaches, we could not confirm a reduction in the incidence of PVL over time.[28 29] However, the recommendation to immediately initiate glucocorticoid therapy on suspicion of GCA is broadly followed by primary care physicians in Switzerland. Therefore, the formal implementation of a fast-track clinic in our hospital in 2014 might not have significantly impacted the speed of the appropriate management of patients with suspected GCA. More difficult healthcare access in other countries, regional differences, smaller sample sizes,[30] potential selection biases due to an increased rate of referrals with less severe manifestations and high numbers of patients with large-vessel GCA,[28–30] as well as different definitions of PVL (we included all patients having experienced PVL within the first 6 months after diagnosis) may explain differences in the impact of fast-track clinics between the cohorts.

In contrast to the effects of fast-track clinics, the management and disease course of patients with GCA before diagnosis have not been studied to date. The time interval from the first symptom to treatment initiation is critical for preventing vision loss. We, therefore, considered both the time from symptom onset to the initial consultation, and the time from initial consultation to therapy initiation for their potential contribution to the development of PVL. Indeed, the time between GCA symptom onset and the first consultation contributed most to the delay in therapy initiation and was the longest in patients with PVL with preceding symptoms.

Five of 43 patients who experienced vision loss before the initiation of treatment had consulted a physician for GCA-related symptoms prior to vision loss but were misdiagnosed. In two of six patients who experienced vision loss after the initiation of glucocorticoid treatment, a GCA diagnosis was made by their primary care provider, but glucocorticoid tapering was inadequate.

Patients without PVL sought significantly earlier medical care. This potentially prevented PVL in some of them. We can only suspect that the non-specific nature of some GCA symptoms precluded some patients from seeking medical attention. Increasing age was associated with PVL in our cohort. Therefore, the older age, associated limited mobility and a potential reluctance to seek medical help may have contributed to the delay between symptom onset and consultation among these patients.

If the diagnosis of GCA was eventually made, therapy was started rapidly, irrespective of the physician's specialisation. This reflects common knowledge among all physicians to immediately start glucocorticoid treatment on suspicion of GCA and then refer patients for further diagnostics.[4 40]

PVL in most cases occurred before presentation to fast-track clinics. Therefore, future strategies for preventing GCA-related damage should focus on the patients' disease course before the referral to fast-track clinics by raising public awareness for GCA. Furthermore, medical education of students and postgraduate teaching of the different presentations and of the adequate treatment of GCA is necessary to prevent misdiagnoses and inappropriate management of patients with GCA.

The major limitation of our study is its retrospective design. Although we found that consultation delay is the longest in patients with PVL with preceding symptoms, specific reasons for the consultation delay remain unknown.

CONCLUSION

PVL was found in 17% of newly diagnosed GCA patients despite recent advances in GCA management and the implementation of fast-track clinics. Older age, jaw claudication and a high number of vasculitis-affected temporal artery segments are associated with PVL. Whereas immediate treatment in case of suspicion of GCA is implemented in general practice, there was still a substantial delay from symptom onset to diagnosis, which was the longest for patients presenting with PVL. Consequently, public and physician awareness of the various

GCA symptoms should be raised. The patient's journey until diagnosis of GCA needs to be further and prospectively studied.

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Contributors Conceptualisation: AKH, MA, SI, SS and TD. Acquisition of data: AKH, MA, NM, PK, SI and SS. Manuscript preparation: AKH, CTB, MA, SI, SS, TD. Preparation of figures and tables: AKH. Statistical analysis: AKH, MA, SI and TD. Interpretation of the data: all authors. All authors commented on the manuscript draft and approved the final version of the manuscript. TD accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Patient consent for publication Not applicable.

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Data availability statement Data are available on reasonable request.

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