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Plasma Viscosity in Giant Cell Arteritis

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Key Words
Giant cell arteritis · Headache · Plasma viscosity · Vasculitis

Abstract
Background: Diagnosis of giant cell arteritis (GCA) is based on criteria of the American College of Rheumatology. However, not all GCA patients meet these criteria and treatment may be delayed in individual patients, leading to an increased risk of complications. ***Methods:*** In an observational study, we investigated acute phase response markers in GCA and non-GCA patients matched for erythrocyte sedimentation rate and CRP levels. ***Results:*** Plasma viscosity (PV) was significantly elevated in all GCA patients, but normal in non-GCA patients. ***Conclusions:*** Our data suggest that PV may reflect a more specific component of the acute inflammatory response in patients with GCA. Analysis of PV may significantly contribute to a reliable diagnosis early in the course of the disease, particularly in patients with suspected GCA that do not meet current diagnostic criteria.

Introduction

Giant cell arteritis (GCA) is a chronic vasculitis of medium- and large-sized arteries that mainly affects elderly persons. Symptoms include headache, jaw claudication, proximal myalgia, weight loss and fever [1]. Acute visual loss is the most dreaded complication and occurs in up to 60% of patients. Early diagnosis and treatment therefore is of utmost importance [2]. Diagnosis is usually established according to criteria of the American College of Rheumatology (ACR). However, up to 25% of GCA patients do not meet these criteria because of negative temporal artery biopsy, normal erythrocyte sedimentation rate (ESR) or atypical clinical presentation [3]. Moreover, about 20% of patients with GCA and visual loss do not present any systemic symptoms of GCA [4]. In these patients, diagnosis and treatment may be delayed.

The aim of the present observational study was to investigate whether plasma viscosity (PV) provides additional diagnostic information in patients with suspected GCA. PV is a hemorheological marker associated with the acute phase response that was repeatedly shown to be elevated in GCA patients [5–7] and in patients with vascular disease [8–10]. Here, PV and inflammatory markers ESR, CRP and fibrinogen were determined in GCA patients and in a sample of patients with various non-rheumatic inflammatory conditions.

Patients and Methods

GCA Patients

Ten consecutive patients with diagnosis of GCA according to ACR criteria, including a positive temporal artery biopsy and/or a halo sign on diagnostic ultrasound, were recruited (7 women; mean age 67.4 years, range 59–77). Temporal artery biopsy was

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Table 1. Clinical characteristics of GCA and control patients

GCA patients			ACR criteria					Ultrasonography
patient	sex	age years	age >50 years	new headache	TA abnormality	ESR >50 mm/h	TAB	
1	f	66	+	+	–	+	–	+
2	f	77	+	+	+	+	+	n/a
3	m	61	+	+	–	+	+	+
4	f	59	+	+	–	+	+	n/a
5	f	60	+	+	–	+	n/a	+
6	f	72	+	–	+	+	+	n/a
7	f	68	+	+	+	+	+	n/a
8	m	71	+	+	–	+	+	–
9	f	69	+	+	–	+	+	+
10	m	71	+	+	–	–	+	+

Control patients			Diagnosis	Antiplatelet treatment
patient	sex	age, years		
1	m	62	*S. aureus* infection, progressive multifocal leukoencephalopathy	–
2	f	68	pneumonia, ischemic pontine infarction	ASA
3	f	71	pneumonia, intracranial hemorrhage	–
4	f	69	pneumonia, intracranial and subarachnoidal hemorrhage	–
5	f	70	community-acquired pneumonia	ASA
6	m	79	urinary tract infection, intracranial hemorrhage	–
7	f	88	upper respiratory tract infection, epilepsy	–
8	f	66	small cell lung carcinoma	–
9	f	70	pneumonia, cardiac arrest	CLP
10	m	68	liver transplantation	–
11	m	54	sepsis, NYHA IV	–
12	f	64	pneumonia, M. Curschmann-Steinert	–
13	m	60	pancreatitis	–
14	f	88	peritonitis	–
15	m	51	sepsis, cervical cancer	–
16	f	66	chordoma surgery	–
17	f	66	hemicolectomy in colorectal cancer	–
18	f	68	coronary artery bypass surgery	ASA + CLP
19	f	74	coronary artery bypass surgery, aortic valve replacement	ASA
20	f	72	coronary artery bypass surgery	ASA

TA = Temporal artery; TAB = temporal artery biopsy; ASA = acetylsalicylic acid; CLP = clopidogrel.

performed in 9 patients within 2 days of admission. A biopsy sample of 10–20 mm length from the left or right superficial temporal artery was taken. Ultrasound of both superficial temporal arteries for detection of a halo sign was performed in 6 patients within 3 days of admission. Clinical details of the patients are summarized in table 1.

Laboratory Investigations

In GCA patients, blood samples were taken on days 1, 5 and 9, including CRP, ESR, fibrinogen and PV. In 1 patient (J.L.), additional investigations were performed on days 2 and 3. PV was measured by means of a capillary viscometer with a disposable polyurethane tube as measuring chamber (Fresenius Medizintechnik, Bad Homburg, Germany).

Treatment

After initial laboratory investigations, patients received steroid treatment. Two patients (R.Z. and I.W.) were treated for 3 days with 500 mg i.v. methylprednisolone, followed by oral methylprednisolone starting with 100 mg on day 4. Eight patients were treated with 100 mg oral methylprednisolone from day 1. The oral methylprednisolone dose was reduced every fourth day by 10 mg.

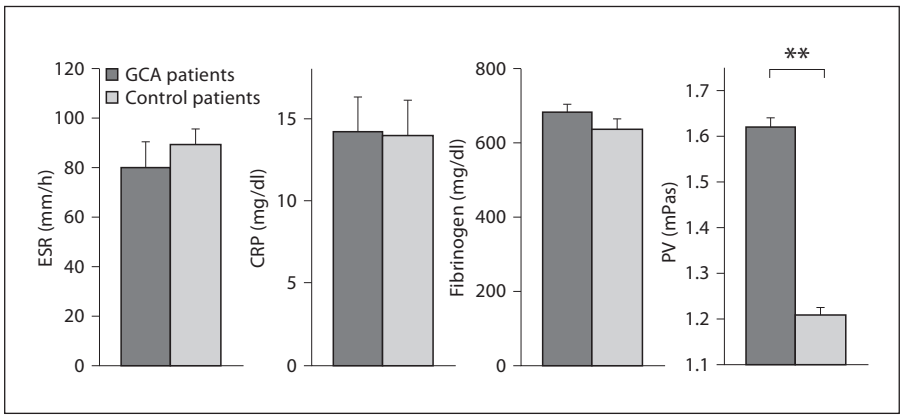

Fig. 1. PV, ESR, CRP and fibrinogen in GCA patients and control patients. Normal ranges in our laboratory were: PV 1.14–1.34 mPas; CRP <0.5 mg/dl; ESR <20 mm/h for men and <30 mm/h for women; and fibrinogen 150–450 mg/dl. ** $p < 10^{-7}$.

Control Subjects

The control group consisted of 20 patients (14 women; mean age 68.7 years, range 51–82) who suffered from nonrheumatic inflammatory diseases or had undergone surgery (table 1). Patients hospitalized at the same time as GCA patients were recruited from the Department of Neurology and interdisciplinary intensive care units of the Charité University Hospital. Patients with steroid medication and rheological treatments were not included. To control for unspecific systemic inflammatory effects on PV, patients were chosen to match GCA patients in terms of age (p = 0.88 difference with GCA patients), ESR (p = 0.98) and CRP (p = 0.73). Six patients received antiplatelet medication.

Standard Protocol Approvals, Registrations and Patient Consents

The study protocol was approved by the local ethics committee on human research. Written informed consent for the use of routine clinical data is part of the standard contract between patients and the Charité Berlin and was obtained from patients or their legal representatives.

Statistical Analysis

Nonparametric statistical tests were applied throughout, i.e. Friedman-ANOVA, Wilcoxon test or Mann-Whitney test [11].

Results

On admission (day 1) CRP, PV and fibrinogen were elevated in all GCA patients (fig. 1). ESR was elevated in all but one GCA patient. In all GCA patients CRP, ESR, fibrinogen and PV varied significantly across the observation period ($p < 0.001$ for all; fig. 2). After 4 days of treatment (day 5), significantly lower values were found for ESR ($p < 0.01$), CRP ($p < 0.001$), fibrinogen ($p < 0.001$) and PV ($p < 0.001$). After 8 days of treatment (day 9), all values showed a further significant decrease compared to day 5 (ESR, $p < 0.01$; CRP, $p < 0.001$; fibrinogen, $p < 0.001$; PV, $p < 0.001$). Before treatment (day 1), PV was elevated in all GCA patients, but within the normal range for all control patients. This group difference was highly significant ($p < 10^{-7}$). PV did not differ significantly between control patients with and without treatment with antiplatelet agents (p = 0.66). Group comparison for fibrinogen before treatment revealed no significant difference (p = 0.08). Further analysis showed a significant correlation between PV and ESR, CRP and fibrinogen for GCA patients (r = 0.76/0.66/0.72; $p < 0.0001$ for all). These correlations were weaker and not significant in control patients (r = 0.14/0.21/0.35; p = 0.56/0.38/0.13; fig. 3).

Although all hemorheological parameters correlated with each other and decreased with treatment in GCA patients, observations in an individual patient suggest that differential sensitivity to disease activity may occur in selected cases. Patient J.L. did not fully comply with oral methylprednisolone treatment because she feared side effects. Here, an increase of PV was observed on day 3 while CRP levels further decreased (ESR was not determined on day 3). In parallel, she reported recurring headache episodes after initial improvement. On day 9, another PV increase was observed relative to day 5, again accompanied by an increase in headache intensity, while CRP and ESR showed a persistent decrease. A similar but less pronounced increase was observed for fibrinogen on day 9.

Discussion

Diagnosis of GCA can pose serious challenges, as the ACR criteria for diagnosis of GCA are frequently not met at initial presentation. Here, we evaluated the utility of PV in comparison to established acute phase response markers for diagnosis of GCA.

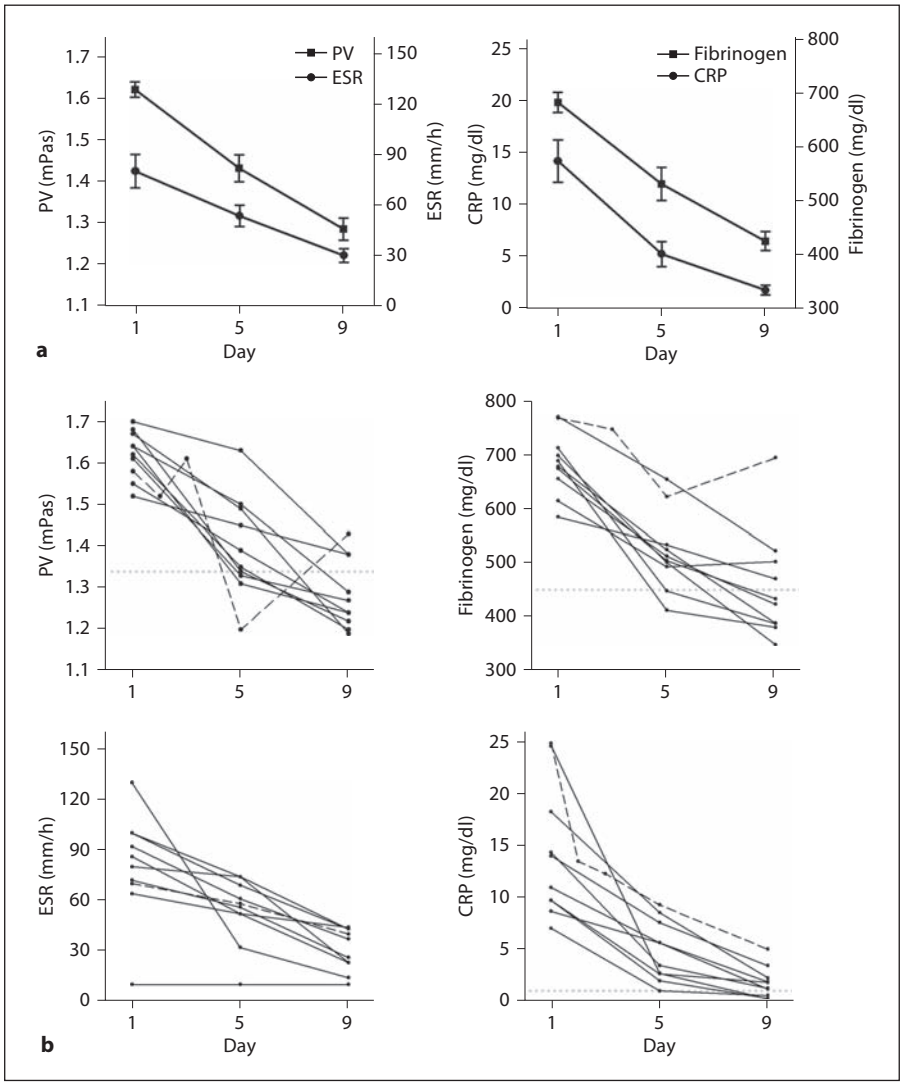

Fig. 2. a Group results for GCA patients for PV, ESR, CRP and fibrinogen on days 1, 5, and 9. **b** Individual data for GCA patients for PV, ESR, CRP and fibrinogen. Dashed line represents patient J.L. Note the increases of PV on days 3 and 9 that were not observed with ESR and CRP.

In many hospitals, ESR is frequently used as an unselective marker of inflammatory disease. Indeed, elevated ESR is one of the five ACR criteria for the diagnosis of GCA. However, in one of our patients ESR was normal. Ellis and Ralston [12] report that 22.5% of their 80 GCA patients presented with a normal ESR. This result delayed therapy in 10 patients and caused serious complications in 4 patients. Other studies found that 5–15% of patients with GCA presented with low ESR (below 40 mm/h) [13]. A further problem is that changes in ESR not only reflect changes in plasma protein, but also changes in hematocrit, red cell deformability and red cell aggregability [14]. Thus, changes in these parameters result in a wide population range of ESR with a poorly defined normal range [14, 15]. In addition, ESR is considerably affected by age, sex, drugs and smoking. By contrast, PV is much less dependent on these factors and has a narrow normal range with well-defined upper and lower limits [5, 14, 15].

CRP is regarded as a valuable addendum to the ACR criteria for the diagnosis of GCA [2]. However, a study by Gudmundsson et al. [6] report that 10% of GCA patients present with normal CRP. Furthermore, PV proved best at predicting flare-ups, while CRP did not. Our observations in patient J.L. are in line with these results. This patient showed two increases of PV levels – most probably due to discontinued steroid therapy – that were not accompanied by increases of CRP or ESR levels, but rather increases in headache intensity.

Comparison of PV between GCA and non-GCA patients suffering from nonrheumatic inflammatory condi-

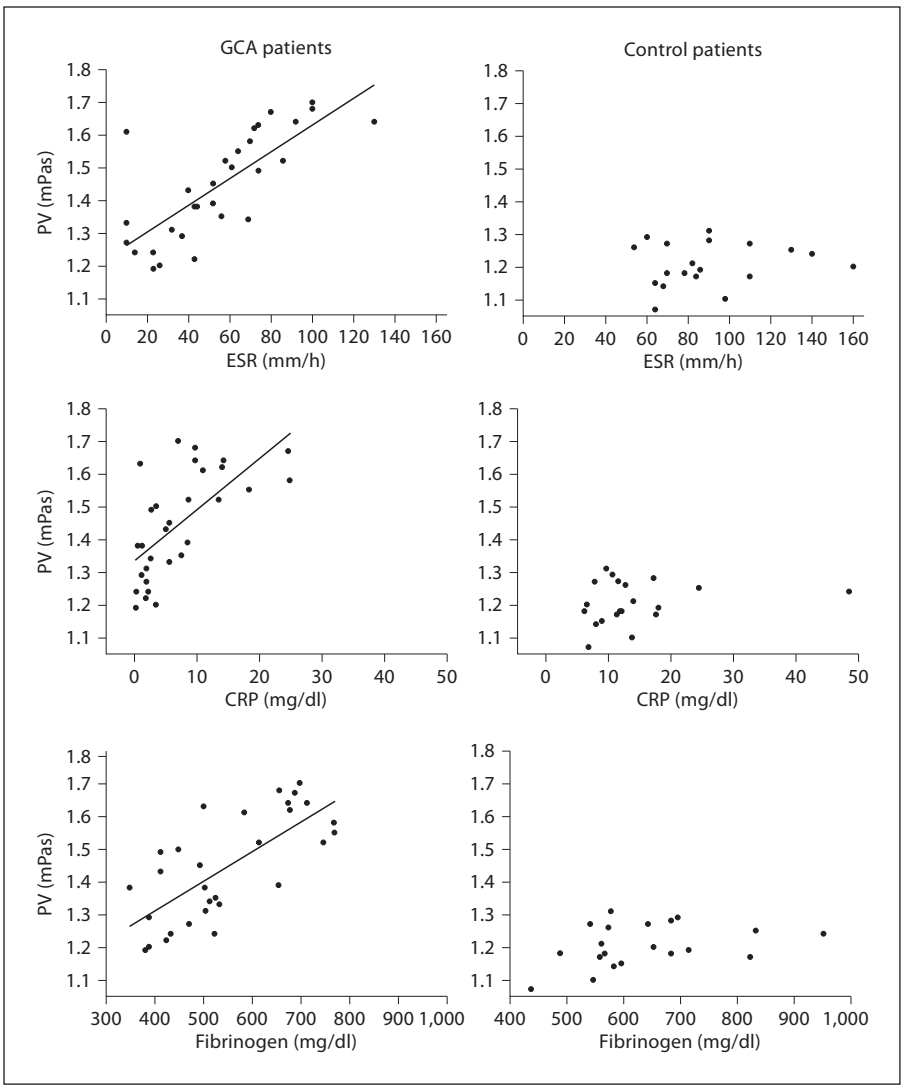

Fig. 3. Correlations between PV and ESR, CRP and fibrinogen for GCA patients and controls. Note the strong positive correlation for PV with ESR, CRP and fibrinogen for GCA patients that is not present in control patients.

tions matched for age, ESR and CRP showed a selective increase of PV in GCA patients. Most notably, PV was within the normal range in control patients despite inflammatory conditions as indicated by raised CRP and ESR. This observation suggests a rather specific response of PV in GCA patients that is absent in other inflammatory conditions, at least in the subjects investigated in the present study. This notion is corroborated by significant correlations of PV with CRP, ESR and fibrinogen in GCA patients, but not in control patients. Hence, CRP, ESR and fibrinogen appear to be elevated in a wider range of inflammatory conditions, while PV appears to be more specific, at least for the comparisons in our study. ESR, CRP, fibrinogen and PV levels do not appear to be interchangeable and unspecific markers of a systemic inflammatory response, but may reflect distinct patterns of hemorheological abnormalities that may help to distinguish GCA from other inflammatory conditions. This may also apply to vascular disorders such as coronary heart disease or stroke since the PV increases observed with vascular diseases (on average +3% compared to controls [8–10]) are far below the substantial increases (+34% compared to controls) observed in our GCA patients.

Taken together, the present results suggest that PV is a laboratory parameter that deserves further investigation for a possible role in the diagnosis of GCA. These investigations are especially warranted as diagnosis of GCA is often delayed in patients with uncommon clinical presentation that do not meet the ACR diagnostic criteria. Although our data suggest a high sensitivity of PV in

GCA, it should be noted that Brittain et al. [5] found a normal PV in 13.3% of patients with biopsy-proven GCA. This discrepancy may relate to the limited number of patients and control subjects in our study and underlines the preliminary character of our findings. Future studies with larger patient cohorts and control subjects with conditions that mimic GCA in clinical presentation may clarify the contribution of PV to early diagnosis of GCA.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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