Joint Bone Spine 84 (2017) 323–326

Available online at
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www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Concise report

Venous thrombosis in patients with giant cell arteritis: Features and outcomes in a cohort study

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ARTICLE INFO

Article history:
Accepted 27 April 2016
Available online 17 June 2016

Keywords:
Venous thrombosis
Giant cell arteritis
Glucocorticoids

ABSTRACT

Objectives: To describe the features and outcomes of patients with giant cell arteritis who developed venous thrombosis.
Methods: Inception cohort study including 428 newly diagnosed patients of giant cell arteritis from 1976 to 2014. Clinical and biological data and outcomes were analysed by comparing patients with and without venous thrombosis.
Results: Twenty-six patients (6%) developed venous thrombosis, 12 of whom presented with pulmonary embolism. The mean time between the onset of giant cell arteritis symptoms and venous thrombosis occurrence was 248.8 ± 215.0 days. No difference was observed between the two groups in clinical or laboratory data collected at diagnosis. The mean time from the start of prednisone to venous thrombosis diagnosis was 187.7 ± 217.0 days. The average dose of prednisone at venous thrombosis onset was 21.5 mg/day. The venous thrombosis group had a higher number of glucocorticoid-related adverse effects (mean, 3.1 vs 1.1; $P < 0.0001$), a higher mortality rate (58% vs 33%, $P = 0.01$) and a higher proportion of deaths occurring during glucocorticoid treatment (31% vs 14%, $P = 0.03$). Death was related to venous thrombosis in four patients.
Discussion: The occurrence of overt venous thrombosis is more than anecdotal among patients treated for giant cell arteritis. Venous thrombosis does not rely on the active phase of giant cell arteritis, but could be associated with long-term use of glucocorticoids. Because venous thrombosis may be associated with an increased mortality risk in patients with giant cell arteritis, a high index of suspicion should be applied in appropriate settings, especially in patients experiencing multiple glucocorticoid-related adverse effects.

1. Introduction

Giant cell arteritis (GCA) is the most common primary vasculitis in persons older than 50 years. It involves the aorta and its branches of the external carotid, especially the extra-cranial branches. Initial symptoms include new-onset headache, jaw claudication, scalp tenderness polymyalgia rheumatica (PMR), and systemic symptoms [1]. Treatment is based on systemic glucocorticoids (GC) that prevent effectively irreversible ischaemic ophthalmologic complications [2]. However, significant toxicity is associated with long-term systemic GC therapy in patients with GCA [3]. Several risk factors of venous thromboembolic disease (VT) may coexist in treated patients with GCA, such as older age, systemic inflammation, and reduced locomotion. In one study of patients with PMR, the risk of pulmonary embolism (PE) increased in the first year after hospital admission with a standardised incidence rate ratio (IRR) of 1.9 [4]. An increased risk of VT was recently reported in patients with GCA with an IRR of 3.58 in the first year of GCA diagnosis [5] and an odds ratio for deep venous thrombosis (DVT) of 2.08 [6]. However, these epidemiologic studies did not provide data regarding GCA presentation and outcomes in patients with GCA who developed VT. Thus, the aim of this study was to describe the clinical and laboratory characteristics in patients with concurrent GCA and VT and the effect of VT occurrence on patient outcomes.

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http://dx.doi.org/10.1016/j.jbspin.2016.04.011
1297-319X/

2. Methods

2.1. Study design

From 1976 through 2014, all patients recruited in the internal medicine department of Limoges University Hospital with newly diagnosed GCA were included in an inception cohort [2]. From 1976 to 1990, we only included patients with biopsy-proven GCA. From 1990, all patients fulfilled the American College of Rheumatology criteria of GCA [7]. Clinical, laboratory, and pathologic data were collected prospectively using a comprehensive questionnaire at the time of diagnosis and during follow-up. We evaluated the delay in diagnosis from the onset of symptoms of GCA, the presence of constitutional symptoms (defined by a body temperature of > 38.2° C for at least 1 week, severe asthenia, or weight loss of > 5%), jaw claudication, PMR, abnormal temporal artery on examination (absence of pulses on all or part of its course, nodules, thickening, swelling, or tenderness on palpation), and upper limb artery involvement (presence of intermittent arm claudication, absent or decreased radial pulse, recent-onset Raynaud's phenomenon, suggestive findings on selective aortic arch arteriography, or a murmur heard over the subclavian–axillary arteries upon admission or within 1 month).

Inflammatory markers including the erythrocyte sedimentation rate and levels of C-reactive protein, fibrinogen, orosomucoid, and haptoglobin were determined prior to GC therapy.

We defined significant inflammatory disease activity as the presentation of symptoms of GCA along with an erythrocyte sedimentation rate and C-reactive protein level of > 50 mm/h and > 25 mg/L, respectively.

GC regimens were different before and after 2002. Before 2002, prednisone was initiated between 0.7 and 1 mg/kg daily and tapered off depending on the opinion of the physician. After 2002, all patients were treated with GC according to the same protocol. While patients without ophthalmological ischaemic complications received prednisone at an initial daily dose of 0.7 mg/kg, those with ischaemic symptoms received a daily dose of 1.0 mg/kg, often preceded by pulse intravenous methylprednisolone (300–1000 mg daily for 1–3 days), according to the severity. When the patient became asymptomatic and the serum C-reactive protein level fell to < 5 mg/L, the prednisone was reduced progressively to 0.35 mg/kg within 4 to 6 weeks, then slowly tapered to achieve a total treatment period of 18 to 24 months. The 3-, 6-, and 12-month doses of prednisone were recorded for each patient. Adverse effects (AEs) of GC were recorded, including infections and cardiovascular, endocrine/metabolic, neuromuscular, skeletal, and gastrointestinal events.

2.2. Diagnosis and documentation of VT

Data concerning potential risk factors for VT (a previous history of venous thromboembolism, varicose veins, heart failure, hypertension, cancer) and some comorbidity factors (diabetes mellitus, dyslipidemia, stroke) were collected for all patients. The diagnosis of VT was established using Doppler ultrasound and/or a ventilation–perfusion lung scan and/or computed tomography. All patients in the VT group received anticoagulation therapy with heparin followed by coumadin or fluindione for 6 (DVT) to 12 months (PE), or continuously in the setting of concurrent cancer.

2.3. Statistical considerations

Statistical analyses were performed to compare patients with GCA with VT (VT group) and without VT (non-VT group) using Student's *t* test for continuous variables and the Chi^2 or Fisher's exact test for proportions. We used logistic regression analysis to determine the impact of VT occurrence on patient outcomes and Kaplan-Meier analysis to compare cumulative survival curves between the two groups. Analyses were performed using Stata, release 5.0 (Stata Corporation, College Station, TX).

3. Results

From January 1976 to December 2014, 428 patients were included in the inception cohort. The mean age at the time of diagnosis was 75.0 ± 7.8 years, and 64% of the patients were female. A total of 27 cases of VT occurred in 26 patients (6%). Among them, 12 patients (46%) presented with PE, which was bilateral in 2 patients. A total of 14 patients (54%) had DVT, and 8 patients had both DVT and PE (31%). A previous history of VT or varicose veins was significantly more common in patients with VT than in patients without VT (15% vs 1.7%, $P = 0.0003$ and 7.7% vs 0.2%, $P = 0.0018$ respectively) (Table 1). Malignancy was observed in six patients with VT and four of them (lung, bladder, colo-rectal and prostate cancer) occurred concomitantly or within 2 months of VT. The mean time between onset of GCA and VT occurrence was 248.8 ± 215.0 days (median, 146 days). As shown in Table 1, no significant differences were observed between the two groups regarding their main clinical and laboratory features at diagnosis. At the time of VT, the mean C-reactive protein was 24.9 ± 27 mg/L (data available for 10 patients). Only one patient in the VT group had an active GCA at the

Table 1
Characteristics of patients in the VT and non-VT groups.

Characterisitics	VT group N (%)	Non-VT group N (%)
Number of patients	26	402
Age in years, mean (range)	75,2 (64–88)	74,9 (51–94)
Sex, women/men	18/8	256/146
Hypertension	9 (34.6)	166 (41.3)
Heart failure	6 (23)	73 (18)
History of VT	4 (15.3)	7 (1.7)[c]
Varicose veins	2 (7.7)	1 (0.2)[b]
Diabetes mellitus	5 (19.2)	33 (8.2)
Dyslipidemia	2 (7.7)	15 (3.7)
Stroke	1 (3.8)	4 (1)
Cancer	6 (23)	54 (13.4)
Fever	12 (46)	184 (45.7)
Weight loss	7 (27)	179 (46.3)
Headache	22 (84.6)	333 (82.8)
Jaw claudication	9 (34.6)	131 (32.5)
Scalp tenderness	9 (34.6)	194 (48.2)
PMR	4 (15.3)	129 (32)
Visual ischaemic events	12 (46)	141 (35)
Upper limb artery involvement	4 (15.3)	48 (12)
Erythrocyte sedimentation rate (mm/1H)	90.8	88.2
C-reactive protein (mg/L)	98.4	97.6
Haemoglobin (g/dL)	11.7	11.4
Platelet count (× 109/L)	418	438
TAB +	21 (81)	294 (73)
Mean 3-month dose of prednisone ± SD (mg/day)	20.32 ± 4.74	19.15 ± 6.31
Mean 6-month dose of prednisone ± SD (mg/day)	14.42 ± 4.86	13.29 ± 4.97
Mean 12-month dose of prednisone ± SD (mg/day)	8 ± 4.41	7.99 ± 4.87
Number of GC adverse effects/patient	3 ± 1.3	1.1 ± 1[c]
GC-induced bone involvement	2/25 (8)	62/359 (17.2)
GC-induced diabetes	9/25 (36)	63/359 (17.5)[a]
GC-induced infections	11/25 (44)	85/358 (23.7)[a]
GC-induced myopathy	7/25 (28)	84/355 (23.6)
Mortality rate	15 (57.7)	128 (31.8)[a]

GC: glucocorticoid; NS: non significant; PMR: polymyalgia rheumatica; SD: standart deviation; TAB: temporal artery biopsy; VT: venous thrombosis.

[a] $P < 0.05$.

[b] $P < 0.01$.

[c] $P < 0.001$.