The different clinical patterns of giant cell arteritis

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ABSTRACT

Objective. *To estimate the frequency of different clinical patterns in giant-cell arteritis (GCA) at onset.*

Methods. *All GCA patients consecutively followed-up in two referral centers for GCA with a biopsy-proven diagnosis and/or large-vessel vasculitis (LVV) demonstrated on imaging were analysed.*

Results. *We analysed the initial clinical presentation of 693 patients with a median age of 75 [48-94] years and including 486 (70%) women. We identified four different clinical patterns: isolated cranial GCA (in 80%), symptomatic LVV with or without associated cranial signs (9%), isolated fever or inflammatory response (9%), and isolated polymyalgia rheumatica with vasculitis (2%). A silent LVV was found in 110 (45%) out of the 247 patients without large-vessel symptoms who underwent imaging at GCA diagnosis. Symptomatic LVV patients were more frequently GC-dependent compared to other patterns (p=0.03) and showed the longest treatment duration (median: 37 [15–212] months versus <30 months for other clinical phenotypes; p=0.001).*

Conclusion. *This study suggests that 80% of GCA patients display a typical presentation, whereas the other 20% showed rarer presentations. Patients with symptomatic LVV required longer treatment duration.*

Introduction

Giant-cell arteritis (GCA) is the most frequent systemic vasculitis in Western countries. Since its first description, multiple clinical and/or radiological sub-phenotypes of the disease have been described. In addition to the typical and pure cranial presentation on which the criteria from the American College of Rheumatology are based (1), other less frequent patterns of the disease have been described (2-4). Large-vessel vasculitis (LVV) has been extensively described in recent years, especially due to the increasing use of whole body imaging such as CT angiography (CTA), magnetic resonance angiography (MRA), and positron emission tomography with computed tomography (PET/CT) (5). Ultrasound is also more widely used in the diagnosis of LVV (6). Other GCA phenotypes, more anecdotally reported and more challenging to diagnose, include GCA with isolated increased inflammatory parameters and/or fever of unknown origin (FUO), GCA with isolated large-vessel involvement without cranial symptoms, and isolated polymyalgia rheumatica (PMR) with LVV or positive temporal artery biopsy (TAB) (2, 7-9). Studies dealing with the frequency of each clinical pattern are scarce, and current knowledge on infrequent spectrums of the disease relies only on small selected series.

In this study, we aimed to determine the frequency of different clinical disease patterns at onset in a large-cohort of consecutive patients with GCA.

Patients and methods

Study population

We enrolled a cohort of newly diagnosed GCA patients recruited from the Internal Medicine departments of two French referral centres for GCA (Limoges and Caen). Patients from Limoges were prospectively enrolled from 1976 until 2017. Records of patients from Caen were retrospectively retrieved from 2000 to 2017 using the hospital diagnostic code database and the register of all temporal artery biopsy (TAB) performed in the hospital. All patients in this cohort were consecutively diagnosed and followed in the departments of Internal Medicine.

All included patients had a biopsy-proven diagnosis (on TAB or extra-temporal artery sample) and/or demonstration of large-vessel vasculitis (LVV) on imaging (without any other cause of LVV).

This study was conducted in compliance with good clinical practices and the Declaration of Helsinki principles. At the time of this study, in accordance with French public health law (Art. L 1121-1-1, Art. L 1121-1-2), formal approval from an ethics committee was not required for this type of observational study that was initiated prior to August 2016.

Study variables and definition

We recorded for each patient demographics, clinical manifestations at onset, laboratory tests at diagnosis, biopsy results, and, when available, the results of large-vessel imaging. Data regarding treatment, the rate of relapses, glucocorticoids (GC)-dependence, GC discontinuation and deaths were retrieved for each patient.

We defined relapse as reoccurrence of symptoms and increased C-reactive protein level that responded to a sustained increase in GC dose. GC-dependence was defined as a daily prednisone dose >0.30 mg/kg after 6 months or >0.20 mg/kg after 12 months, or failure to withdraw GC treatment after 24 months.

In light of published series, we distinguished four main clinical patterns according to the clinical manifestations at onset (1, 2, 7, 9). Cranial GCA involved patients with isolated cranial symptoms affecting the cranial area (*e.g.* headaches, scalp tenderness or jaw claudication), *i.e.* without extracranial vascular features suggesting LVV. Patients with cranial symptoms and clinically silent LVV on imaging were classified as having cranial CGA. The 2nd clinical pattern included patients with symptomatic LVV such as limb claudication or pulseless limb. Patients with isolated raised inflammatory markers and/or fever of unknown origin (inflammation or fever of unknown origin: IFUO) formed the 3rd pattern. The 4th pattern included patients with clinically isolated PMR but with vasculitis demonstrated on TAB or imaging.

Statistical analyses

Categorical variables were expressed as numbers (%), and quantitative variables were expressed as medians [range]. Quantitative variables among the four subgroups were analysed using the Kruskal-Wallis test. For categorical analysis, the Chi-square for trend was used. The statistical analyses were computed using JMP 9.0.1 (SAS Institute Inc., Cary, NC, USA). A $p \leq 0.05$ defined statistical significance.

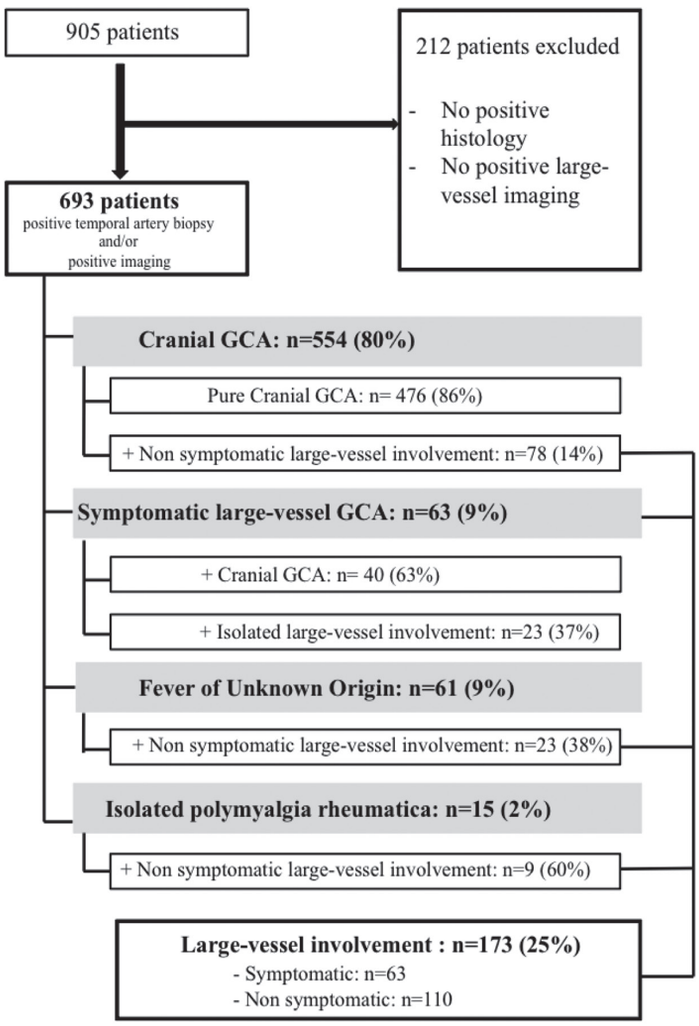

Fig. 1. Flow-chart of patients' selection and details of the four identified clinical patterns.

Results

Description of the four clinical patterns

We analysed the initial clinical presentation of 693 patients with a median age of 75 [48–94] years and including 486 (70%) women. Figure 1 depicts the flow-chart of patients' selection and sub-grouping. GCA diagnosis was made on biopsy in 632 (91%) patients. The 61 remaining patients without biopsy-proven diagnosis had demonstration of LVV on imaging (aortic CTA, MRA and/or PET/CT imaging).

Figure 1 and Table I show the main characteristics of the four clinical patterns at diagnosis, namely, isolated cranial GCA (in 80%), symptomatic LVV (in 9%) with or without associated cranial signs, GCA as IFUO (in 9%) and GCA as isolated PMR (in 2%).

A silent LVV was found in 110 (45%; 78 with cranial GCA + 23 with IFUO + 9 with isolated PMR) out of the 247 patients without large-vessel symptoms who underwent imaging. The proportions of the four clinical patterns between patients from both centers did not differ (p=0.45).

Treatment and outcomes

The initial GC doses or the relapse rates did not differ between the four groups. Symptomatic LVV patients were more

Table I. Disease patterns in 693 patients with giant-cell arteritis.

	Isolated cranial GCA (n=554)	Symptomatic large-vessel GCA (n=63)	GCA as isolated IFUO (n=61)	GCA as clinically isolated PMR (n=15)	*p*-value
Demographics					
Female	378 (68)	52 (83)	45 (74)	11 (73)	0.11
Age	76 [51-94]	70 [53-92]	72 [48-89]	77 [58-83]	<0.0001
Cardiovascular risk factors					
Hypertension	258 (47)	32 (51)	22 (36)	9 (60)	0.24
Tobacco use	62 (11)	10 (16)	8 (13)	0	0.34
Diabetes mellitus	55 (10)	3 (5)	8 (13)	2 (13)	0.43
Dyslipidaemia	85 (15)	7 (11)	12 (20)	4 (27)	0.37
Delay to diagnosis, days	45 [2-580]	100 [0-1825]	95 [21-380]	165 [50-420]	<0.0001
Clinical manifestations at onset					
Fever	168 (30)	22 (35)	37 (63)	2 (13)	<0.0001
Headaches	491 (89)	35 (56)	-	-	<0.0001
Scalp tenderness	291 (53)	14 (22)	-	-	<0.0001
Jaw claudication	255 (46)	12 (19)	-	-	<0.0001
Ophthalmic troubles	207 (37)	8 (13)	-	-	<0.0001
Unilateral blindness	106 (19)	4 (6)	-	-	<0.001
Bilateral blindness	26 (5)	0	-	-	0.08
Polymyalgia rheumatica	206 (37)	18 (29)	-	15 (100)	<0.0001
Limb claudication	0	56 (89)	-	-	<0.0001
C-reactive protein, mg/l	83 [1—535]	58 [3—300]	119 [18—382]	66 [22—229]	0.004
Mean to diagnose GCA					
Positive histology	528 (95)	44 (70)	50 (82)	10 (67)	<0.0001
LVV on imaging	78/199 (39)	63 (100)	23/39 (59)	9/9 (100)	<0.0001

Except where indicated otherwise, values are displayed as absolute number (%) or median [range].
GCA: giant-cell arteritis; IFUO: inflammation or fever of unknown origin; PMR: polymyalgia rheumatica; TA: temporal artery; LVV: large-vessel vasculitis.

Table II. Treatment and outcomes of patients with GCA according to different disease patterns.

	Isolated cranial GCA (n=554)	Symptomatic large-vessel GCA (n=63)	GCA as isolated IFUO (n=61)	GCA as clinically isolated PMR (n=15)	*p*-value
GC dose, mg/k					
At onset	0.73 [0.25-1.6]	0.7 [0.38-1.15]	0.7 [0.3-1.1]	0.7 [0.63-1]	0.56
At month 12	0.1 [0.01-00.36]	0.12 [0.03-0.53]	0.14 [0.06-0.29]	0.13 [0.04-0.29]	0.11
Discontinuation of GC	296 (53)	33 (52)	26 (43)	5 (33)	0.20
Duration of GC, month	23 [3-133]	37 [15-212]	27 [10-97]	30 [19-71]	0.001
Relapse	276 (50)	40 (63)	31 (51)	7 (47)	0.23
GC-dependence	161 (29)	29 (46)	15 (25)	4 (27)	0.03
Use of GC-sparing agent	92 (17)	16 (25)	13 (22)	3 (20)	0.31
Follow-up, months	50 [0-279]	76 [0-264]	28 [0-139]	27 [1-142]	0.0008
Death	163 (29)	18 (29)	20 (31)	1 (7)	0.25

Except where indicated otherwise, values are displayed as absolute number (%) or median [range].
GCA: giant-cell arteritis; IFUO: inflammation or fever of unknown origin; PMR: polymyalgia rheumatica; GC: glucocorticoids

frequently GC-dependent compared to other patterns (p=0.03) and showed the longest treatment duration (median: 37 [15–212] months *vs*. <30 months for other clinical phenotypes; p=0.001). At last follow-up, 360 (52%) patients had discontinued their treatment permanently (Table II).

Discussion

Distinguishing and comparing GCA patients according to these four clinical patterns at onset had not been reported previously. This classification appears clinically relevant and practical. Isolated cranial form remains the most frequent and typical clinical pattern (80% of patients) with the highest risk for early ischaemic complications, especially visual loss, as previously described (10, 11).

Our study is the first to report such a high number of patients with symptomatic LVV in a cohort of consecutive GCA patients. Owing to the study design without selection bias, the proportion of patients with symptomatic LVV is probably representative of a clinically relevant subgroup of the disease. In a well-defined cohort of 168 consecutive patients diagnosed with GCA in Olmsted County (Minnesota) between 1950 and 1999, 21 (13%) incident cases of large-artery stenosis occurred, without focus of the initial clinical pattern (12). LVV was observed in all four clinical

patterns but was often non symptomatic, as in the literature where 30% to 80% of assessed patients are described with silent LVV (2, 13). Herein, we found a 45%-rate of silent LVV in GCA patients who underwent large-vessel imaging at diagnosis. Previous studies highlighted the need to revisit and redefine the concept of the disease, especially regarding the inclusion of LVV in ACR criteria (2).

The link between PMR and GCA is not fully elucidated, although many studies suggest a strong relationship between the two conditions (8, 13, 14). There are several reports of patients diagnosed with PMR without any signs of GCA who subsequently developed GCA many months to years after (14, 15). Blockmans *et al*. showed, in a PET/CT study performed in patients with isolated PMR, that large vessels were involved in 31% of the cases (14). Whether patients with initial PMR and subsequent vasculitis must be retrospectively upgraded in GCA at disease onset remains unclear. Indeed, our 15 patients with clinically isolated PMR did not respond to low GC doses usually able to control PMR and required at least 0.7 mg/kg/day of prednisone to achieve complete and durable control. These findings suggest that the end of the spectrum of PMR may be GCA.

Our study has several limitations, including its retrospective design. The different times of diagnosis between both centers are probably another limitation as patients included before 2000 might have had less easy access to imaging. Recruitment of patients in internal medicine departments may have led to overestimate the proportion of patients with atypical presentations such as IFUO and symptomatic LVV. Only 45% of the patients underwent routine large-vessel imaging, which may have introduced selection biases. Moreover, as most of our patients had a biopsy-proven diagnosis, the proportion of LVV in our cohort may be underestimated as some studies suggested a lower rate of positive TAB in patients with LVV (7).

In conclusion, according to our study design, typical GCA and atypical presentations of GCA account for 80% and 20% of the cases, respectively. Further pathophysiological studies are needed to analyse whether different mechanisms support these different phenotypes. Finally, therapeutic studies are required to determine whether these different clinical patterns warrant different therapeutic approaches.

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