Upper respiratory tract and orofacial manifestations of new-onset giant cell arteritis: results from a large, prospective inception cohort study

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Abstract

Objective

Giant cell arteritis (GCA) often features upper respiratory tract (URT) and orofacial manifestations, which signal the involvement of external carotid artery branches. In this study, we aimed to describe the frequency of various URT/orofacial symptoms at GCA onset, as well as the main characteristics of patients presenting these symptoms.

Methods

We included all patients who were newly diagnosed with GCA between 1976 and April 2022 at the Internal Medicine Department of a tertiary-care hospital. Ten URT or orofacial symptoms were prospectively examined systematically in each patient. We used multivariate analyses to identify the GCA characteristics, including URT/orofacial symptoms, associated with temporal artery biopsy (TAB) positivity.

Results

At least 1 URT/orofacial symptom was present in 68.6% of the 599 patients (3 or more symptoms in 30% of cases). Jaw claudication, maxillary pain, and pain during mouth opening were the most prevalent symptoms. Dry cough was recorded in 17% of cases. GCA patients with URT/orofacial symptoms had more clinical abnormalities of the temporal artery bed and ischaemic ophthalmological complications, but less large-vessel vasculitis according to imaging. The likelihood of a positive TAB was increased in patients with an abnormal temporal artery upon clinical examination (OR 4.16; CI 2.75–6.37, p<0.001) or jaw claudication (OR 2.18; CI 1.35–3.65, p=0.002), and decreased in those with hoarseness (OR 0.47; CI 0.26–0.87, p=0.02) or earache (OR 0.54; CI 0.31–0.95, p=0.03). Isolated URT/orofacial presentation (i.e. without headache or visual signs) accounted for 5.2% of the entire cohort.

Conclusion

Oral-facial symptoms were present in two-thirds of GCS cases. Thus, they could serve as leading clinical clues for a GCA diagnosis, and are a risk factor for permanent visual loss. Several URT/orofacial symptoms such as jaw claudication, hoarseness, and earache influenced the likelihood of a positive TAB. Isolated URT/orofacial presentation of GCA is a rare but potentially challenging occurrence.

Key words

giant cell arteritis, ear nose throat, cough, hoarseness, jaw claudication

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Introduction

Giant cell arteritis (GCA) is the most prevalent form of systemic vasculitis in patients over 50 years old. It affects the aorta and supra-aortic vessels, especially the external carotid artery and its branches (1). Contemporary studies on the clinical expression of GCA tend to classify patients into four main groups based on the following symptoms: constitutional syndrome (sometimes leading to biological inflammation or fever of unknown origin), cranial signs (headache, scalp tenderness, jaw claudication, and ophthalmic manifestations), large-vessel inflammatory signs, and polymyalgia rheumatica (PMR) (2). Ischaemic stroke and visual impairment (classically caused by anterior ischaemic optic neuropathy) are the main causes of disability among patients with GCA (1, 3).

Upper respiratory tract (URT) and orofacial (*e.g.* extending from the zygomatic region to the supraglottic zone) symptoms are common in GCA patients because the condition is known to affect virtually all external carotid artery tributaries (1). The first description of GCA-related URT/orofacial manifestations may date back to the fourteenth century B.C., with the report of a blind harpist, Pa-Eton-Em-Eb, who had swollen eyelids and a dark line on the temporal zone (4). Starting in the 1930s and continuing throughout the twentieth century, descriptions of jaw claudication became increasingly frequent in Horton reports (5, 6). Despite this, few systematic reports have evaluated these manifestations (7-10), although some have explored specific signs of GCA such as jaw claudication (11).

To address this issue in the present study, we examined patients included in an historic inception cohort of new-onset GCA to determine the frequencies and disease associations of various URT/orofacial manifestations using data prospectively obtained via a fixed questionnaire.

Methods

Study design and population

We included all consecutive patients diagnosed with GCA from 1976 through May 2022 at the Internal Medicine Department of a tertiary-care teaching hospital. Before 1990, GCA was diagnosed based on clinical presentation, the presence of acute phase reactants, and rapid, sustained response to glucocorticoid treatment. A pathological temporal artery biopsy (TAB) specimen was also obtained from most early patients. Starting in 1990, GCA was diagnosed based on the criteria of the American College of Rheumatology (ACR) (12). It was considered to be present in biopsy-negative cases if at least three of these criteria were fulfilled or if two criteria were fulfilled and aortic computed tomography angiography (CTA) or fluorodeoxyglucose (FDG)-positron emission tomography (PET/CT) indicated evidence of aortitis (13). Aortitis was defined for the CTA as a circumferential and homogeneous thickening ≥2 mm of the vascular wall, and for the PET/CT as a vascular uptake equal or superior to the liver physiologic uptake (13). In biopsy-proven cases, GCA was pathologically confirmed via temporal artery biopsy using currently accepted criteria (14). Clinical, laboratory, and pathological data were prospectively recorded at the time of first admission using a specifically designed 176-item questionnaire to collect the detailed history and log data. All study data were stored in computerised files and regularly updated (15).

We included all patients newly diagnosed with GCA for whom orofacial symptoms were prospectively collected. Patients with incomplete data pertaining to URT/orofacial manifestations were excluded from the study.

Clinical and laboratory data

The questionnaire assessed the presence of 10 systematically collected URT/orofacial symptoms or signs including facial or eyelid swelling, jaw claudication, pain and/or difficulty opening the mouth (up to complete trismus), maxillary or dental pain, pharyngeal pain, sore throat, dry cough, hoarseness, earache, and tongue pain. Symptoms were identified as specific to GCA because they were recent in onset, concomitant with the other signs of GCA and regressed after the introduction of corticosteroid therapy. With regard to facial oedema, patients' physical examination and laboratory tests

ruled out heart failure or chronic kidney disease. GCA patients without headache or visual signs who recalled at least 1 of the abovementioned symptoms/signs and met at least three of the ACR-1990 (12) and/or the achievement of a total score of 6 or greater EULAR/ACR-2022 criteria (16) were defined as having a pure URT/orofacial presentation. Other clinical variables compiled from the computerised files included polymyalgia rheumatica, general signs, scalp tenderness, new headache, and fever. A decreased or absent pulse, beaded and/or indurated artery, local redness, or tenderness were sufficient to characterise a temporal artery as abnormal. Constitutional syndrome was defined as a temperature of at least 38°C for more than a week, associated with severe asthenia and/or weight loss of at least 5%. Biological data included erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP) and fibrinogen levels, and complete blood counts. Cardiovascular comorbidities included diabetes, dyslipidaemia, stroke, carotid stenosis, lower extremity artery disease, and heart attack. Patients were considered to have acute presentation of GCA if they were able to indicate the day the symptoms began. Ischaemic complications related to GCA included permanent visual loss (anterior or posterior ischaemic optic neuropathy, central retinal arterial occlusion) that was confirmed by ophthalmology staff, ocular nerve palsy, symptomatic axillary/subclavian or femoral/iliac stenosis, and non-embolic stroke occurring in the acute phase of the vasculitis. Aortitis was diagnosed via PET/CT scans if they showed a strong, linear uptake of the aortic wall, superior to the liver uptake (13). Patients with large-vessel involvement without aortitis (subclavian/axillary, carotid and/or iliac/femoral arteries) demonstrated on imaging were included. Less than 50% of the GCA patients in our cohort have had a temporal artery ultrasound doppler examination. Older examinations are not always available to verify results. Moreover, other branches of the external carotid artery (*e.g.* the facial artery) are very rarely explored in our centre. For these reasons, we do not report the ultrasound data in this study.

Treatment

Treatment was based on a standardised corticosteroid regime with prednisone at a starting dose of 0.6–1 mg/kg/day, depending on the clinical severity of the disease. Patients without ischaemic complications were eligible to receive a daily dose of 0.6–0.8 mg/kg until they were asymptomatic with a normalised CRP level, at which point the dose was progressively decreased to 0.35 mg/kg/d over 4 to 6 weeks. Patients with ischaemic visual impairment or threat such as amaurosis fugax and abnormal eye fundus, or an altered ophthalmic artery according to ultrasound Doppler analysis, were initially treated with prednisone at a dose of 0.9–1mg/kg/d. This was often preceded by pulsed high-dose methylprednisolone, which was then progressively reduced in a similar fashion to that described above. The initial therapeutic phase started on the first day of steroid therapy (including methylprednisolone IV pulses), followed by a tapering phase from the first dosage decrement to planned cessation.

Statistical analyses

The data were extracted and analysed retrospectively from information initially collected prospectively from the patient charts. We compared the frequency of occurrence of each URT/orofacial symptom. We also compared the clinical and laboratory characteristics of patients with URT/orofacial symptoms with those of the rest of the cohort.

For descriptive analysis, continuous quantitative variables were represented as means and standard deviations (SD), and qualitative variables were represented as percentages. We used Pearson's χ^2 test to compare qualitative variables between groups of patients. To compare quantitative variables between groups, we used the Kruskal-Wallis test. After univariate logistic regression analyses of the diagnostic predictive factors of a positive TAB, variables with a *p*-value less than 0.25 were included in a multivariate logistic model. The quantitative variables used to test the Logit linearity hypothesis were integrated without modification. The initial multivariate model was simplified via stepwise backward elimination so that the final model included only variables significantly associated with the target variable. Model calibration was assessed using Pearson residual tests. Tests were 2-sided and a p-value <0.05 was considered to be significant. All calculations were performed using R software v. 3.2.2 (R foundation for Statistical Computing, Vienna, Austria).

Ethical approval and informed consent

All patient data were retrospectively collected using a prospective questionnaire for GCA patients. This study was, therefore, conducted in compliance with the Good Clinical Practice and Declaration of Helsinki principles. In accordance with French law, formal approval from an ethics committee and written informed consent were not required for this type of retrospective study, provided that each patient had not exercised their right to reject participation in a study. Informed consent was obtained from all individual participants included in the study, including their informed consent for publication of images possibly involved.

Results

Patient characteristics

The inception cohort included 641 patients who sought treatment between 1976 and April 2022. We excluded 42 patients (6.6%) for whom we had insufficient information about URT/orofacial manifestations. A total of 599 patients (429 biopsy-proven GCA, 71.6%) met the entry criteria. Most (64.9%) were women, and the average age of the cohort was 75.0 (69.5–80.0) years. Over four-fifths (81.3%) of the patients experienced headache, and this was mostly in the temporal region (68.3%). The temporal artery appeared abnormal on palpation in 58.9% of the patients. Aortic imaging was performed in 175 patients (29.2%, 67 PET/CT and 108 CTA), and evidence of aortitis was detected in 66 (37.7%) patients. The average follow-up time was 62 months.

Characteristics of GCA patients with oral-facial symptoms/signs

Among the cohort, 411 patients (68.6%) had at least 1 URT/orofacial manifestation. Most of these patients had only

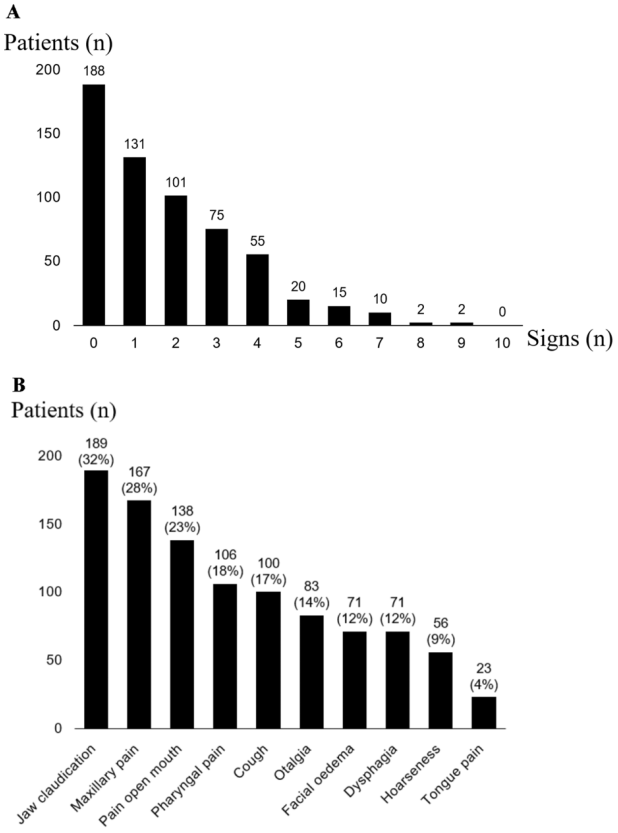

Fig. 1. A: Patient distribution according to number of URT/orofacial symptoms and signs in a cohort of 599 GCA patients.
B: Frequency and distribution of ten upper respiratory tract and orofacial manifestations in the 599 GCA patients.

1 (131/411, 31.9%) or 2 (101/411, 24.6%) symptoms (Fig. 1A). Jaw claudication, maxillary pain, and pain upon mouth opening were the most frequent symptoms (32%, 28%, and 23%, respectively, among the entire cohort) (Fig. 1B). As depicted in Table I, we found no differences in age, sex, or the presence of cardiovascular comorbidities according to the presence of URT/oral-facial symptoms/signs. Patients with orofacial manifestations were more likely to have an acute presentation of the disease (48.3% *vs*. 34.1%, p=0.001), with a shorter time to diagnosis (95.3±100.6 days without, 71.4±77.1 days with URT/orofacial manifestations, p=0.038). URT/orofacial manifestations were more frequent in individuals with clinical abnormalities including temporal artery palpation (70.4% *vs*. 33.9%, p<0.001), new-onset headache (89.2% *vs*. 64.9%, p<0.001), and ischaemic complications (42.7% *vs*. 29.8%, p=0.004), and less frequent in those with large-vessel vasculitis according to imaging data (29.0% *vs*. 58.8%, p<0.001). Inflammatory biomarker levels (ESR, CRP) were similar in both groups. Less deaths were observed during the follow-up of patients with URT/orofacial manifestations (37.2% *vs*. 48.9%, p=0.018; follow-up: 58.9 *vs*. 69.2 months, p=0.094).

Comparison of GCA patients with orofacial manifestations according to TAB results

Among the GCA patients with URT/orofacial manifestations, those with a positive TAB result were more likely to have an abnormal temporal artery examination. Jaw claudication was significantly more frequent in TAB-positive patients (53.9% *vs*. 27.8%, p<0.001). In the multivariate analysis, hoarseness and otalgia were associated with a lower TAB positivity rate. Ischaemic complications, such as permanent ischaemic blindness, were more common in TAB-positive patients. We found no differences in the other ischaemic complications or inflammatory biomarkers.

Characteristics of patients with isolated orofacial symptoms/signs at GCA onset

Table III summarises the findings from patients with a pure orofacial presentation. Of the 31 patients, who represented 5.2% of the entire cohort and 7.5% of the patients with at least 1 orofacial symptom, 23 met the ACR-1990 criteria and 29 met the ACR/EULAR-2022 criteria. The average age at diagnosis was 75 years, with a median time to diagnosis of nearly 117 days. Cough was the most frequently encountered symptom (17 cases, 55%), followed by maxillary (9 cases, 29%) and pharyngeal pain (8 cases, 26%). These were mostly inflammatory forms (average CRP, 105 mg/L; average ESR, 83 mm/h). Aortitis was documented in 11 cases, but was seldom searched for in this patient subset. TAB specimens were positive in most cases (84%). All three biopsy-negative cases fulfilled the ACR criteria (either 1990 or 2022).

Characteristics of GCA patients according to the presence of jaw claudication

Men made up slightly more than half of the patients with jaw claudication (or pain upon mouth opening) at diagnosis, although we found no differences in cardiovascular comorbidities. Patients with jaw claudication were more likely to present with local inflammatory temporal artery signs (78.1% *vs*. 44.2%, p<0.001), headache (93.8% *vs*. 72.2%, p<0.001), scalp tenderness (67.1% *vs*. 35.9%, p<0.001), and to have positive TAB specimens (83.3% *vs*. 66.8%, p<0.001). However, large-vessel vasculitis was more prevalent in patients who did not recall jaw claudication (49.1% *vs*. 20.3%, p<0.001). There were no differences in biological inflammatory parameters according to the presence of jaw claudication.

Comparison of GCA patients according to the presence of dry cough

There were no significant differences in the mean delay in diagnosis, age, sex, cardiovascular comorbidities, or frequency of positive TAB specimens between patients with versus those without dry cough. Patients with dry cough had a greater prevalence of pharyngeal and ear pain, and underwent aorta imaging more frequently (46.4% *vs*. 28.5%, p<0.001). However, the rate of aortitis detection was the

Table I. Comparison between GCA patients with and without URT/orofacial symptoms and signs.

	GCA without URT sign 188 (31.3)	GCA with URT signs 411 (68.6) n (%) or mean [standard-deviation]	*p*-value
Demographics and comorbidity			
Gender (male)	70 (37.2)	140 (34.1)	0.5077
Age (years)	74.4 (8.9)	74.8 (7.5)	0.6624
Cardiovascular comorbidity	96 (51.9)	243 (59.7)	0.0907
GCA presentation and symptoms			
Diagnosis delay (days)	95.3 [100.6]	71.4 [77.1]	0.0377
Hospital delay (days)	19.1 [45.5]	7.8 [31.4]	<0.0001
Acute onset GCA	63 (34.1)	195 (48.3)	0.0010
ACR 1990 criteria (/5)	3.6 [0.9]	4.3 [0.9]	<0.0001
≥3 ACR 1990 criteria	184 (97.9)	390 (94.9)	0.0904
Constitutional syndrome	130 (69.1)	319 (78.2)	0.0228
Fever	77 (41.4)	166 (41.0)	0.9967
Abnormal TA palpation	63 (33.9)	285 (70.4)	<0.0001
Headache	122 (64.9)	365 (89.2)	<0.0001
Temporal headache	97 (51.6)	312 (76.7)	<0.0001
Scalp tenderness	53 (29.6)	235 (58.5)	<0.0001
Occipitalgia	60 (32.4)	229 (56.4)	<0.0001
Polymyalgia rheumatica	60 (31.9)	119 (29.0)	0.5231
Large-vessel involvement			
Aorta imaging	51 (30.9)	124 (32.7)	0.7525
Aortitis at diagnosis	30/51 (58.8)	36/124 (29.0)	0.0002
Superior limb arteritis	32/51 (62.7)	30/124 (24.2)	<0.0001
Inferior limb arteritis	10/51 (19.6)	12/124 (9.7)	0.0718
Complication			
Ischaemic complication	56 (29.8)	175 (42.7)	0.0035
Visual symptom	43 (22.9)	162 (39.6)	0.0001
Fugax amaurosis	24 (12.8)	120 (29.6)	<0.0001
Permanent amaurosis	23 (12.2)	67 (16.4)	0.2331
Bilateral amaurosis	5 (2.7)	19 (4.6)	0.3560
Stroke	9 (4.8)	12 (2.9)	0.3608
Temporal artery biopsy			
Positive results	125/178 (70.2)	304/402 (75.6)	0.2064
Biology			
ESR (mm)	86.8 [30.3]	85.0 [28.8]	0.4603
CRP (mg/L)	89.0 [62.3]	96.9 [67.3]	0.2486
Fibrinogen (g/L)	6.5 [1.8]	6.9 [1.7]	0.0405
Platelet (G/L)	415.3 [159.8]	439.4 [150.2]	0.0385
Treatment			
Bolus	30 (16.0)	124 (30.2)	0.0003
Initial glucocorticoids dose (mg/kg/d)	0.7 [0.2]	1.0 [2.9]	<0.0001
Dose M6 (mg/d)	12.1 [5.4]	12.2 [4.5]	0.9979
Dose M12 (mg/d)	6.9 [4.7]	7.0 [4.1]	0.5529
Sparing treatment	41 (21.8)	79 (19.2)	0.6635
Evolution			
Follow-up (month)	69.2 [59.6]	58.9 [49.4]	0.0942
Relapses	102 (57.0)	225 (57.0)	1.0000
Death during follow-up	92 (48.9)	153 (37.2)	0.0176

GCA: giant cell arteritis; URT: upper respiratory tract and orofacial manifestations; ACR: American College of Rheumatology; TA: temporal artery; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

same between both group (44.2% *vs*. 35.0%, p=0.247). Patients with a cough at diagnosis had a lower mortality rate (29.1% *vs*. 44.2%, p=0.004), despite a similar length of follow-up (56.8 *vs*. 63.4 months, p=0.641).

Discussion

Cranial symptoms (*e.g*. new headaches, abnormal temporal artery palpation) are the best known, and easily evoke GCA after the age of 50. URT/orofacial manifestations are sparsely detailed in the literature and less familiar to clinicians. However, these symptoms/signs should suggest GCA, because of the risk of irreversible ischaemic complications due to delayed diagnosis. A simple upper respiratory infection or other chronic systemic diseases (*e.g*. Wegener's granulomatosis, relapsing polychondritis) present similar URT/orofacial symptoms/signs and are sometimes difficult to distinguish from GCA. It is therefore important to always keep these differential diagnoses in mind.

We focused on these manifestations to highlight their frequency and associated features in a large cohort of GCA patients. In the present study, 68.6% of patients had at least 1 URT/orofacial symptom, with jaw claudication as the most prevalent. Jaw claudication is considered to be the most particular symptom (6), and was thus included in the EULAR/ACR-2022 criteria (16). Jaw symptoms in GCA patients comprise not only jaw claudication, but also jaw stiffness or difficulty during mouth opening, 'lockjaw' (so-called trismus) (17), maxillary pain, and toothache. These miscellaneous symptoms are less typical than classic jaw claudication, and are not well-known to physicians. Thus, this lack of awareness may contribute to diagnostic delays in some patients (18). Overall, we found that jaw symptoms were the most frequently reported signs by our patients (54%). Jaw claudication reflects stress-induced ischaemia of the masseter and temporalis muscles (11), and is often the only URT/orofacial symptom assessed in cohorts of GCA patients (10, 19). In the present study, jaw claudication was slightly less prevalent (31.5%) than in other studies (36–47%) (10, 16, 19-21). The difference may likely to be due to the use of a strict definition and a prospective questionnaire in the present study. Another hypothesis is that the difference is due to the inclusion criteria used. Jaw claudication is a cranial manifestation of the disease, and therefore is more frequent in patients with cranial-GCA, who frequently have a positive TAB, than in patients with LV-GCA, who frequently lack cranial symptoms and have a negative TAB (22). Studies including only cranial-GCA patients have higher

Table II. Characteristics of patients with URT/orofacial symptoms and signs-according to result of temporal artery biopsy.

Only GCA with URT signs	Negative TAB n 98	Positive TAB 304 n (%)	*p*-value
URT symptoms			
Number of URT signs	2.5 (1.6)	2.6 (1.7)	0.3258
Jaw claudication	27 (27.6)	164 (53.9)	<0.0001
Hoarseness	22 (22.4)	38 (12.5)	0.0259
Dysphagia	12 (12.2)	64 (21.1)	0.0738
Tongue pain	2 (2.0)	21 (6.9)	0.0817
Otalgia	27 (27.6)	60 (19.8)	0.1397
Cough	34 (34.7)	81 (26.6)	0.1601
Pain opening mouth	31 (31.6)	106 (34.9)	0.6418
Maxillary pain	44 (44.9)	126 (41.6)	0.6459
Facial oedema	16 (16.3)	56 (18.4)	0.7499
Pharyngal pain	27 (27.6)	85 (28.0)	1.0000

URT: upper respiratory tract and orofacial manifestations; GCA: giant cell arteritis; TAB: temporal artery biopsy.

prevalence of jaw claudication compared to studies (including the present) in which both cranial and LV-GCA patients are included. Clinical characteristics, treatment and prognosis of two population-based cohorts of patients with biopsy-proven GCA from Minnesota, USA and Italy were compared (23). Jaw claudication was reported in 42.7% of patients from USA and 52.1% of those from Italy. Different studies showed that patients presenting with jaw claudication are at higher risk of vision loss, and therefore these patients may require a higher initial dosage of glucocorticoids (24).

Maxillary pain, which was also frequently reported by our patients, can be distinguished from jaw claudication by its continuous or rapid onset at meal uptake and its occurrence during specific chewing phases. Maxillary pain can lead to trismus (17, 21). Differential diagnosis with respect to neuralgia or temporo-mandibular joint disorder can be challenging, especially in older patients with a coincidental poor dental condition (25). Unfortunately, this can result in unjustified dental extractions (26, 27).

Dry cough appears to be the foremost respiratory sign of GCA (28-30). Although the underlying mechanisms have not been clearly identified, dry cough could be mainly related to the presence of aortitis or, in rare cases,

Table III. Pure URT/orofacial form characteristics: GCA with URT signs and without headache and visual symptoms.

≠	Age/ sex	Signs	Time before diagnosis	CRP (mg/L)	ESR (mm)	Aortis	TAB result	Initial CS dose (mg/kg/d)	Sparing treatment	Relapse	ACR 1990	ACR/ EULAR 2022
1	81M	Maxillary pain, pharyngal pain	55	172	105	ND	-	0,7	No	Yes	2	5
2	78F	Pharyngal pain, cough, otalgia	125	47	68	ND	-	0,7	No	Yes	2	5
3	81F	Cough	50	39	46	ND	+	0,68	No	No	2	7
4	77F	Cough	175	10	20	Yes	+	0,9	No	No	2	8
5	84F	Cough, hoarseness	50	111	111	No	-	0,74	No	Yes	3	8
6	83M	Maxillary pain, pharyngal pain, cough, hoarseness	95	68	48	Yes	+	0,71	No	No	2	8
7	57F	Cough	75	151	115	Yes	-	0,75	No	Yes	2	9
8	67M	Cough	365	36	69	Yes	-	1,05	TCZ	No	2	9
9	68F	Cough	175	10	29	Yes	+	1	No	No	2	11
10	76F	FO, POM, dysphagia	45	158	90	ND	+	1	No	No	3	11
11	68M	Cough,hoarseness	82	21	66	Yes	+	0,65	No	Yes	3	12
12	86F	JC, maxillary pain	4	ND	ND	ND	+	0,35	No	Yes	3	13
13	67F	Cough	35	300	120	ND	+	0,7	No	Yes	3	14
14	78F	Cough	70	180	86	ND	+	0,7	No	No	3	14
15	75F	Cough	430	130	75	ND	+	0,7	MTX	Yes	4	14
16	71M	Dysphagia	45	58	96	ND	+	1	No	Yes	4	14
17	78F	Dysphagia, hoarseness	220	28	64	ND	+	0,7	TCZ	No	3	14
18	78M	FO	150	66	102	ND	+	0,8	No	Yes	3	14
19	81F	FO, pharingal pain	45	71	60	ND	+	0,65	No	ND	3	14
20	67F	JC, maxillary pain, dysphagia, otalgia	425	114	90	ND	+	0,7	No	Yes	3	14
21	82F	JC, POM, maxillary pain	21	ND	83	ND	+	0,7	No	No	3	14
22	75F	POM, otalgia	60	144	87	ND	+	0,68	No	Yes	4	14
23	68F	Cough	180	86	103	Yes	+	0,8	No	No	3	15
24	80F	FO, maxillary pain, otalgia	45	140	98	Yes	+	0,75	No	Yes	3	15
25	82F	JC, maxillary pain, pharyngal pain, cough	125	80	87	Yes	+	0,67	No	No	3	15
26	68M	Pharyngal pain, cough, hoarseness	60	107	78	Yes	+	0,7	No	No	3	15
27	70F	JC, pharyngal pain, dysphagia, cough	210	ND	ND	ND	+	0,83	No	Yes	3	16
28	73M	Cough, hoarseness	95	154	106	ND	+	0,97	TCZ	No	4	17
29	83F	FO, JC, POM, pharyngal pain, dysphagia, tongue pain	21	89	82	No	+	1	No	No	3	17
30	84F	JC, maxillary pain	70	218	98	No	+	0,69	No	Yes	4	17
31	72M	Maxillary pain, otalgia	26	165	116	Yes	+	0,7	TCZ	Yes	4	18

GCA: giant cell arteritis; URT: upper respiratory tract and orofacial manifestations; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; TAB: temporal artery biopsy; CS: corticosteroids; ACR: american college of rheumatology; EULAR: European Alliance of Associations for Rheumatology; M: male; F: female; ND: not done; TCZ: tocilizumab; MTX: methotrexate; FO: facial oedema; JC: jaw claudicatio; POM: pain when opening mouth; +: positive TAB result; -: negative TAB result.

pulmonary or pleural disorders (29, 31-38). In the present study, we did not identified association between dry cough and aortitis. However, the patients with dry cough underwent thoracic imaging more often than the other patients, limiting the value of this finding. Medium- and large-vessel pulmonary artery inflammation and the granulomatous involvement of peribronchial vessels could explain the occurrence of dry cough in untreated GCA patients (29, 39). Other URT symptoms such as sore throat and hoarseness are not as well-known as cough in this patient group. Although these symptoms may obscure GCA diagnosis when isolated or prominent, they can provide useful clues when associated with headache or visual impairment (29). Although hoarseness is thought to be caused by ischaemic damage to branches of the external carotid arteries supplying blood to laryngeal muscles, in rare cases it may signal laryngeal recurrent nerve compression via a thoracic aortic aneurysm (40, 41). Hoarseness may precede or occur at the same time as visual symptoms, and Chean *et al*. found that a high proportion of patients with visual symptoms of GCA also had hoarseness (42-44). Sore throat and dysphagia were commonly reported by our patients, and these were often part of a larger URT/orofacial symptomatic complex. The inflammatory involvement of ascending pharyngeal arteries is a plausible explanation for these throat features (29, 45). Facial (or orbital and eyelid) swelling was also relatively frequent, but these data were often anamnestic (46). This highlights the value of using a fixed, prospective GCA questionnaire that includes items about rare symptoms.

We found a higher incidence of jaw claudication in TAB-positive patients, which was consistent with previous reports (47-49). Gonzaley-Gay *et al*. found that jaw claudication was almost twice as frequent in an inception cohort of patients with TAB-positive GCA (47). We also found that positive TAB specimens had an unprecedented negative relationship with hoarseness and earache, two symptoms that have not been consistently described in GCA patients. Although we do not have an explanation for this intriguing finding, GCA patients may have various patterns of external carotid branch involvement, despite the lack of overt temporal artery vasculitic injury. The lower prevalence of temporal artery abnormalities and greater fatigue in the negative biopsy group is in line with previous observations by Koster *et al*. (49).

Importantly, the systematic use of a fixed, comprehensive questionnaire enabled us to define a small clinical subset (around 5%) characterised by the presence of orofacial manifestations in the absence of usual cranial manifestations of GCA such as headache and visual disturbances. In this setting, diagnosis can be very challenging, and requires a high level of familiarity with the protean clinical manifestations of GCA. This can be facilitated by meticulously tracking patient history using specialized tools, such as our questionnaire. Interestingly, subclinical aortitis was identified in 11 out of 14 (79%) patients with pure URT/orofacial presentation. Although patients with this unusual presentation were more likely to undergo thoracic imaging than patients with a more typical presentation, the high frequency with which we identified aortitis in these patients may point to an association between certain URT/orofacial symptoms, notably dry cough, and aortitis.

The unsolved questions regarding the pathological mechanisms underlying the URT/orofacial manifestations of GCA emphasise the need for a more targeted method of imaging the arteries belonging to the external carotid system. While ultrasound scanning of the temporal artery constitutes a cornerstone in the routine diagnosis of GCA, explorations of the maxillary artery appear to be of growing interest (50, 51). Sammel *et al*. found that PET-CT had a sensitivity of 92% and a negative predictive value of 98% compared with TAB (52). However, these results should be interpreted with caution, as the TAB positivity rate was only 21% and the study did not compare these techniques with temporal artery ultrasound, which is more sensitive than a positive TAB result in the diagnosis of GCA (53). Looking for the halo sign on the facial and occipital arteries also helped identify a few more cases of GCA that were undiagnosed according to TAB specimens and temporal artery ultrasound (54). Magnetic resonance imaging (MRI) could also be an interesting method to evaluate inflammatory damage of the external carotid territory (*e.g*. facial, occipital, maxillary arteries).

The presence of blood acute phase reactants (*e.g*. elevated ESR and CRP) could assist GCA diagnoses in all cases, especially difficult ones, and could also facilitate the diagnoses of other serious conditions such as regional infection and necrotising vasculitides (55). In particular, granulomatosis with polyangiitis, which has similar symptoms to GCA, should be carefully ruled out when a patient with suspected GCA displays a myriad of URT/orofacial symptoms and/or shows an inadequate response to glucocorticoid treatment (56, 57). More recently, COVID-19 has emerged as an alternative diagnosis, especially in patients with respiratory signs (58). Jaw claudication is a more specific symptom of GCA, even in TAB-negative cases (49). Nevertheless, TAB should be systematically considered in patients over 50 years old who display an oral or respiratory presentation (mostly protracted dry cough) and persistent raised acute phase reactants, especially as some diseases may mimic GCA and ultrasound halo signs (59).

The shorter diagnostic delay in patients with URT/orofacial symptoms may be related to more frequent and more suggestive classical clinical symptoms (headache, temporal artery abnormalities, scalp tenderness), as well as a greater proportion of patients with acute onset and a lower frequency of those with systemic presentations. These data corroborate a previous meta-analysis, which reported a mean diagnostic delay of 7.7 weeks for patients with cranial patterns, compared with 17.6 weeks for patients without cranial symptoms (60). The shorter duration of symptoms before GCA diagnosis also applied to patients with jaw symptoms, especially jaw claudication. Moreover, consistent with our observations, several studies have shown that jaw claudication is

associated with a higher TAB positivity rate (61). That relationship does not appear to be influenced by the intensity of the acute phase reactants, as demonstrated by Gonzalez-Gay *et al*. (62). Although cardiovascular risk factors may increase the incidence of ischaemic complications in patients with GCA, no significant association with jaw claudication has been established (63).

In the present study, we found that patients with URT/orofacial symptoms/signs initially received higher dosages of corticosteroid therapy. This difference in therapeutic approaches could be related to a higher frequency of permanent ophthalmological ischaemic complications and ischaemic jaw claudication in this patient subset. Although French recommendations favour an initial prednisone dose of 0.7 mg/kg in patients without ischaemic complications, the higher incidence of ischaemic complications among patients with jaw claudication may justify increasing the initial prednisone dose to 1 mg/kg in anticipation of these symptoms (64). This reflects the American guidelines for newly diagnosed GCA patients (65).

The present study has some limitations that should be noted. Some orofacial symptoms reported in the literature, such as trismus, hypogeusia, hearing loss, and pre-auricular oedema (7), were not included in our questionnaire and thus not systematically reported. Furthermore, some symptoms such as trismus were investigated long after the study onset, which may have led to an underestimation of their frequency. We acknowledge that TAB were not reviewed by a pathologist and we did not collect the histological details of TAB. Additionally, a large proportion of patients (mostly in the early period of study) did not undergo imaging of the aorta, which could lessen the accuracy of the association between URT/orofacial symptoms and aortitis. Aortic imaging was not systematically reviewed by a radiologist/nuclear medicine physician, which could explain the low rate of aortitis detected in this study. Moreover, we have no information on how many patients were already on steroids at large-vessel imaging. Lastly, the present study did not include dedicated imaging of CE branches other than the temporal arteries. These techniques are now more readily available, and could support mechanistic explanations for a number of URT/orofacial symptoms. Despite these limitations, the large sample size of GCA patients included in this study and the systematic use of a comprehensive forward-looking questionnaire allowed us to create a large and accurate dataset that enabled the description and quantification of a rare form of isolated URT/orofacial GCA. The present study also offers new insights regarding previously known symptoms such as jaw claudication and dry cough.

Conclusion

We present the first observational study of GCA patients to include most of the possible URT/orofacial symptoms. Our dataset clarifies the frequency and wide diversity of these symptoms. Cephalic GCA without headache or visual manifestations can be difficult to diagnose, and differential diagnosis with a number of other conditions including necrotising vasculitides must be quickly established. Our findings can aid early diagnosis by quickly signalling the likelihood of GCA. Furthermore, the relationship between jaw claudication and cranial ischaemic complications in GCA could be a starting point for considering higher doses of glucocorticoids, although further prospective studies are needed to support this idea.

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