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RESEARCH LETTER

Cranial versus Extracranial Involvement in Giant Cell Arteritis: 15 Years Retrospective Cohort Analysis

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Giant cell arteritis (GCA) is a medium-large systemic vasculitis presenting primarily in patients over 50 years. It usually involves carotid artery branches, especially the temporary artery; nevertheless, it can affect the arterial wall of other large and medium arteries.[1] Cranial manifestations are the most frequent and usually define the study.[2] Extracranial involvement, otherwise frequent, can modify clinical and diagnostic features of the disease and may need higher levels of suspicion and other diagnostic strategies to address territories involved.[3] Reports regarding extracranial involvement in GCA vary depending on the diagnostic method used, ranging from 3% to 92%. Using angiography, the prevalence ranges from 20% to 67%; on the other hand, positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) shows 83% and 92%.[3,4] Up to 77% of these patients are asymptomatic and present isolated extracranial involvement.[5] The most frequently affected extracranial sites are the carotid, subclavian, axillary, and thoracic aorta, which can be complicated with dissection and aneurysms of the affected arteries.[4]

There are some comparative series between cranial involvement patients and those with extracranial involvement; nevertheless, those do not include Latin American population-based cohorts, including clinical, imaging, and biopsy features.[6–8] In a 15-year retrospective cohort study including the aforementioned aspects, we analyzed differences between patients diagnosed with GCA with cranial involvement and patients who had extracranial arteries affected. The latter were diagnosed upon presentation with systemic inflammatory symptoms in the absence of demonstrable infectious disease, persistently elevated inflammatory parameters, vascular symptoms and/or older age (>55 years old). We were able to gather 26 patients with cranial – and no extracranial – involvement defined by clinical aspects, imaging, and biopsy and compare it with eight patients with extracranial involvement (Table 1), including demographic, clinical, physical examination, imaging, biopsy findings, treatment, and follow-up (Table 2).

Cranial and extracranial involvement groups were demographically homogeneous; nevertheless, headache, a cornerstone in clinical diagnosis, resulted significantly less common in extracranial involvement patients exposing the importance of keeping higher levels of suspicion (Table 2). Laboratory findings regarding inflammatory parameters were similar in both groups; however, creatinine and urinary nitrogen levels were significantly more elevated in the extracranial group, almost doubling creatinine values in the latter. No renal artery compromise was found on an imaging study, considering that those patients do not undergo more sensitive study strategies as angiographic study (Table 2). With all this information, interestingly, half of the patients with extracranial involvement did not meet ACR criteria,[9] exposing a big issue: Do these criteria allow us to diagnose patients without temporal artery compromise accurately? In our patients, lack of headache and negative artery biopsy prevented them from fitting the criteria. Biopsies in both groups have the same histologic findings, suggesting no differences in the pathogenic process (Table 2).

In terms of treatment, both groups responded adequately to high doses of corticosteroids and according to reported rates. Remarkably, even when there is no more relapse in either cranial or extracranial involvement group, time to remission was significantly higher in the latter (Table 2).

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Table 1 Extracranial Involvement in Patients' Clinical and Laboratory Features

Patient	Gender	Age at Diagnosis	Clinical Presentation	Presenting Symptoms	Temporal Biopsy	ESR at Presentation*	Reactive C Protein at Presentation+	Topographic Pattern
1	F	58	GCA + EC	VASCULAR CLAUDICATION	NOT DONE	55	23	DTA, AA, LAA, RAA, LCA, LSA, RSA, IA
2	F	85	GCA + EC	FUGAX AMAUROSIS	NOT DONE	87	59	ATA, DTA, AA, LAA, RAA, LCA, LSA, RSA, IA
3	F	74	GCA + EC	HEADACHE/SS	TRANSMURAL INFLAMMATION/GIANT CELLS	60	154	ATA, DTA, AA, LCA, RCA, LSA, RSA, MA, IA
4	F	68	GCA + EC	HEADACHE/SS	TRANSMURAL INFLAMMATION/GIANT CELLS	120	356	LCA, RCA, LSA, RSA, VA
5	F	60	EC ALONE	FUO/ POLYMYALGIA	ATHEROSCLEROSIS	120	300	DTA, AA, MA
6	M	80	EC ALONE	THORACIC PAIN	NORMAL	69	45	ATA, DTA, AA, LCA, RCA, LSA, VA
7	M	57	EC ALONE	SS	NORMAL	130	217	ATA, DTA, AA, MA
8	M	66	EC ALONE	FUO	NOT DONE	40	31	MA

Notes: *mm/hr. +mg/l. Using computed tomography angiogram and Doppler ultrasound confirmation (with GCA protocol).

Abbreviations: SS, systemic symptoms; FUO, fevers of unknown origin; GCA, giant cell arteritis; EC, extracranial involvement; ESR, erythrocyte sedimentation rate; ATA, ascending thoracic aorta; DTA, descending thoracic aorta; AA, abdominal aorta; LAA, left axillary artery; RAA, right axillary artery; LCA, left carotid artery; RCA, right carotid artery; LSA, left subclavian artery; RSA, right subclavian artery; MA, mesenteric artery; IA, iliac artery; VA, vertebral artery.

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Table 2 Cranial and Extracranial Groups' Comparative

	Group 1	Group 2	p-value[+]
	GCA – Cranial Involvement (N = 26)	GCA – Extracranial Involvement (N = 8)	
Demographic			
Age, years ± SD	72 ± 8.6	68 ± 7	NS
Men, %	19	27	NS
Female, %	81	63	NS
Disease characteristics			
Time to diagnosis, months ± SD	3.5 ± 2.4	3.6 ± 2.5	NS
Symptoms and signs			
Fever, %	34	30	NS
Weight loss, %	40	50	NS
Malaise, %	50	63	NS
Night sweats, %	3	0	NS
Headache, %	73	38	p=0.023
Headache duration, months ± SD	3.2 ± 2.3	3.4 ± 1.8	NS
Arthralgia, %	50	50	NS
Myalgia, %	28	25	NS
Amaurosis fugax, %	20	13	NS
Bilateral vision loss, %	20	0	NS
Diplopia, %	7	0	NS
Mandibular claudication, %	43	50	NS
Presentation			
Fever of unknown origin, %	10	13	NS
Rheumatic polymyalgia, %	30	13	NS
Laboratory Findings			
Hemoglobin, g/dl	11.8 ± 1.4	10.3 ± 2.3	NS
Hematocrit, %	36.8 ± 4.8	33.2 ± 6.7	NS
Leucocytes, cells/mm3	9074 ± 2788	8215 ± 1530	NS
Platelets, cells/mm3	336671 ± 151091	275800 ± 136736	NS
Erythrocyte sedimentation rate, mm	88.4 ± 29.2	84.8 ± 37.1	NS
C-reactive protein, ug/mL	122.8± 86.7	148 ± 130	NS
Creatinine, mg/dl	0.78 ± 0.19	1.11 ± 0.48	p=0.0014
Blood urea nitrogen, mg/dl	16.1 ± 4.6	23.1 ± 10.8	p=0.042

(*Continued*)

Table 2 (Continued).

	Group 1	Group 2	p-value[+]
	GCA – Cranial Involvement (N = 26)	GCA – Extracranial Involvement (N = 8)	
Diagnostic Features			
Meet Chapel Hill criteria, %	67	75	NS
Meet ACR criteria, %	77	50	p=0.018
Imaging			
AngioTC findings, %	20	100	p=0.0001
Intrathoracic, % (of positive AngioTC)	50	87.5	NS
Extra thoracic, % (of positive AngioTC)	50	12.5	NS
Biopsy			
Biopsy findings, %	87	75	NS
Mononuclear infiltrate[¥], %	100	100	NS
Granulomas[¥], %	4	16	NS
Giant cells[¥], %	27	33	NS
Treatment Features			
Methylprednisolone bolus, %	27	38	NS
High dose prednisone (1mg/kg), %	83	62	NS
Corticoid-sparing medication, %	73	75	NS
Achieve remission, %	73	88	NS
Time to remission, % (less than three months)	91	72	p=0.032
Time to remission, % (more than three months)	9	18	NS
Relapse, %	46	56	NS
Time to relapse, % (less than three months)	33	50	NS
Time to relapse, % (more than three months)	67	50	NS

Notes: [¥]Percentage from positive biopsies. [+]Analysis performed using t-student.

Considering all this information, some aspects are important: There is no indication of differences in pathogeny between these two types of involvement, as was demonstrated in similar findings in biopsies from both groups. Nevertheless, the clinical course could be different and lead to misdiagnosis or difficulties in suspicion of the disease. Clinical presentation could miss critical symptoms, and temporal biopsy is informed negative, even having systemic inflammation and other large arteries being compromised. Given the frequent compromise of extracranial and cranial territories simultaneously, we should be vigilant, beyond the ACR criteria, of systemic symptoms or fevers of unknown origin in younger patients, which available classification criteria could miss. Given this, it is essential to keep higher suspicion of extracranial involvement in patients presenting with non-infectious inflammatory disease, with high levels of erythrocyte sedimentation rate and C-reactive protein.

Ethics Approval

This study was approved and conducted in compliance with the Declaration of Helsinki. Hospital Clinico de la Universidad de Chile's Scientific Ethics Committee. Acta N°: 46 on September 5th, 2019 approved this study.

Individual informed consent was not asked since all the data was extracted and processed anonymously from digital clinical charts.

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