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Comparison of cranial and extra-cranial involvement of patients with giant cell arteritis

Dev hücreli arteritte kraniyal ve ekstra-kraniyal tutulumların karşılaştırılması

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Abstract

Objective: Giant cell arteritis (GCA) is a chronic granulomatous inflammation of medium and large sized arteries; it is also known as temporal arteritis. The aim of the study was to investigate the clinical, laboratory and radiological findings of the patients diagnosed with GCA and to compare cranial, extra-cranial (ECI) and either involvement patterns.

Methods: The study was designed as cross-sectional. The demographic and clinical data, laboratory results, imaging and biopsy findings were documented. The patients were divided into three groups according to the involved regions.

Results: Twenty-four patients with GCA were evaluated. When patients were divided into three groups as cranial (CI), ECI and both cranial and extra-cranial (CECI) involvement; vision loss, jaw claudication, scalp tenderness, temporal artery stiffness, tenderness and pulselessness were common in patients with CI. Weight loss was significantly higher in patients with ECI than in patients with CI. Positron emission tomography (PET) was performed in 50% of GCA patients; vasculitic involvement was found in all of the 5 patients with ECI and CECI, whereas it was not observed in 7 patients with CI.

Conclusion: GCA is a vasculitis that is among the large vessel vasculitides, but until recently, its CI findings were better defined than its systemic involvement. With the widespread use of modern imaging techniques, ECI involvement accompanying CI involvement and isolated ECI involvement has been better defined. Constitutional symptoms and positive PET findings were more prominent in patients with ECI, which is thought to be related to systemic disease pattern.

Keywords: Giant cell arteritis, temporal arteritis, cranial, extra-cranial, imaging, positron emission tomography

Öz

Amaç: Dev hücreli arterit (DHA), orta ve büyük çaplı arterlerin kronik granülomatöz enflamasyonudur; temporal arterit olarak da bilinir. Çalışmanın amacı DHA tanısı konulan hastaların klinik, laboratuvar ve radyolojik bulgularının araştırılması ve kraniyal (CI), ekstra-kraniyal (ECI) ve her iki bölgede tutulum paternlerinin karşılaştırılmasıdır.

Yöntem: Çalışma kesitsel olarak tasarlanmıştır. Demografik ve klinik veriler, laboratuvar sonuçları, görüntüleme ve biyopsi bulguları kaydedilerek, hastalar tutulum bölgelerine göre üç gruba ayrılmıştır.

Bulgular: DHA'lı yirmi dört hasta değerlendirildi. Hastalar CI, ECI ve kraniyal ve ekstrakraniyal (CECI) tutulum olarak üç gruba ayrıldığında; görme kaybı, çene kladikasyosu, saçlı deride hassasiyet, temporal arterde sertlik, hassasiyet ve nabızsızlık CI grubunda daha yaygındı. Kilo kaybı ECI'lı hastalarda CI'lı hastalara göre anlamlı olarak daha yüksekti. Pozitron emisyon tomografisi (PET), DHA hastalarının %50'sine çekilmişti; ECI ve CECI'lı 5 hastanın tümünde vaskülitik tutulum bulunurken, CI'lı yedi hastada tutulum gözlenmedi.

Sonuç: DHA, büyük damar vaskülitleri arasında yer alan bir vaskülittir ancak yakın zamana kadar kraniyal bulguları sistemik tutulumdan daha iyi tanımlanmıştır. Modern görüntüleme tekniklerinin yaygınlaşması ile kraniyal tutulumlara eşlik eden ECI tutulumlar ve izole ECI tutulumlar daha iyi tanımlanmıştır. Konstitüsyonel semptomlar ve pozitif PET bulguları ECI olan hastalarda daha belirgin olup, bu daha sistemik bir hastalık paterni ile ilişkili olarak değerlendirilmiştir.

Anahtar Kelimeler: Dev hücreli arterit, temporal arterit, kraniyal, ekstra-kraniyal, görüntüleme, pozitron emisyon tomografisi

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Introduction

Giant cell arteritis (GCA) is a chronic granulomatous arteritis of medium and large sized arteries; it is also known as temporal arteritis.[1] It is more common in females, with an incidence ratio of approximately 2-3:1. GCA affects people over 50 years old, and the disease peaks between the ages of 70-79.[2] Constitutional symptoms, headache, jaw claudication, tenderness in the scalp, visual findings, musculoskeletal system involvement are common.[3] Polymyalgia rheumatica (PMR) often coexists with GCA, seen in approximately 40 to 50 percent of patients.[4] Although the temporal arteries are the most commonly affected vessels in GCA; the carotid arteries, vertebral arteries, subclavian, axillary and proximal brachial arteries, the ascending aorta and coronary arteries may be affected.[5] With the widespread use of positron emission tomography (PET) in patients with GCA and PMR, the frequency of observation of extra-cranial involvement (ECI) accompanying cranial involvement (CI) or isolated ECI has increased.[6] In this study, we compared the clinical, laboratory and imaging findings of patients with different involvement patterns.

Materials and Methods

Study Design and Study Population

The study design was cross-sectional. The medical records of all patients with GCA followed up between January 2010 and September 2021 at Kocaeli University Hospital, Clinic of Rheumatology, were reviewed. The patients who fulfilled the American College of Rheumatology 1990 GCA classification criteria were included the study.[7] The local ethics committee of Kocaeli University approved the study protocol (date: 13.09.2021, approval number: 2021/232).

Data Collection

The demographic and clinical characteristics, including age, gender, symptoms, disease duration, physical examination findings at the time of diagnosis, laboratory, imaging and biopsy results, and treatments, were obtained from medical records. Laboratory results at the time of diagnosis, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count and lipid levels were recorded. The findings of imaging modalities, including temporal artery ultrasonography (USG), PET/computed tomography (PET/CT), thorax and abdominal magnetic resonance (MR) angiography and CT angiography, and cranial MR imaging were noted.

PET/CT Analysis Method

PET imaging was performed with a GE healthcare discovery PET/CT 690 scanner using F-18 fluorodeoxyglucose as a radiopharmaceutical. Images were obtained from the hospital PACS system.

Statistical Analyses

Statistical analysis was performed by SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to evaluate the demographic variables and clinical data. The normality of continuous variables was checked by Shapiro-Wilk test. In numerical data, mean and standard deviation for normal distributions and median (IQR) for non-normal distributions were given. Group comparisons were made by Kruskal-Wallis H and ANOVA test for continuous variables and chi-square test for categorical variables.

Results

The data of 24 patients with the diagnosis GCA were analyzed. Thirteen (54%) of these patients were female. The mean age at diagnosis was 72.4±8.75 years. The median disease duration was 33 (14.3-83) months and the median time between the onset of symptoms and the diagnosis of disease was 1 (0-4.8) month.

Constitutional symptoms were present in 11 (46%) patients. Among the common symptoms of GCA; the most common was visual loss, observed in 18 (75%) patients, followed by headache in 13 (54%), scalp tenderness in 9 (37.5%) and jaw claudication in 9 (37.5%). In the temporal artery examination, 6 (25%) patients had tenderness, 3 (13%) had stiffness and 7 (29%) had temporal pulselessness. In one patient who described extremity claudication, there was a lack of pulsation in the left upper extremity and a blood pressure difference between the extremities; and this patient had both CI and ECI. Two (8.3%) patients had a murmur in the branches of the aorta and 2 (8.3%) had an abdominal aortic aneurysm.

The PMR findings were accompanied in 25% of the patients with GCA. The mean ESR was 72.64±25.48 mm/h, and median CRP level was 50.5 (19.2-128) mg/L. All patients had elevated ESR and CRP values. There were no patients whose ESR and CRP values were within normal limits at the time of diagnosis. No difference was found between the presence of PMR and ESR or CRP elevation (p=0.538, p=0.193; respectively).

Temporal artery USG was performed in 15 (62.5%) patients, and halo sign was observed in 20% of these 15 patients. In 2 (8.3%) patients, intima media thickness compatible with vasculitis was observed in carotid Doppler USG. The vasculitic involvement was detected in 5 (20.8%) of 12 patients in whom PET/CT was performed. All of these 5 patients had thoracic aorta involvement, 3 patients had involvement of the aortic arch and its branches, 3 patients had abdominal aorta involvement, and 2 patients had a femoral artery involvement. Supratentorial and periventricular white matter T2 hyperintense foci, which may be compatible with vasculitis, were detected in 7 of 10 (41.6%) patients in whom cranial MR imaging was performed. Vasculitic involvement was seen in 2 of 7 (29.2%) patients who underwent thoraco-abdominal MR angiography. In these 2 patients, celiac artery and superior mesenteric artery were affected. No significant involvement was observed in 2 (8.3%) patients who underwent thoraco-abdominal CT angiography.

Temporal artery biopsy (TAB) was performed in 14 (58.3%) patients and the diagnosis was confirmed by biopsy in 13 (54.1%) of them. Among these 14 patients who had TAB, all of them had CI involvement. TAB was not performed in 3 patients with cranial symptoms in the cranial and extra-cranial involvement (CECI) group, the diagnosis was confirmed by imaging. One patient was diagnosed with GCA after total hysterectomy and salpingo-oophorectomy. Non-necrotizing vasculitis characterized by giant cells and granulomas on the walls of myometrial tubal and ovarian small to medium sized arteries were found in the pathology specimen. This patient had no cranial symptoms, large vessel vasculitis was also confirmed by PET/CT.

Hypertension, which is the most common comorbidity, was present in 17 (71%) patients, 7 (29.2%) patients had diabetes mellitus and 7 (29.2%) patients had coronary artery disease. The demographic and clinical data of the patients were given in the Table 1.

Among the 24 patients followed up with the diagnosis of GCA, 18 had isolated CI, 3 had ECI, and 3 had CECI. These 3 groups were compared in terms of clinical, radiological findings and treatment regimens they received. However, statistics could not be made because the number of patients in the groups was low (Table 2). There was no difference between the groups in terms of age at the diagnosis, time from onset of symptoms to diagnosis, gender, and smoking habits. Constitutional symptoms and weakness were more common in patients with ECI. Weight loss was detected more frequent in the ECI group than in the CI group. Vision loss, jaw claudication, scalp tenderness, temporal artery stiffness, tenderness and pulselessness were common in patients with CI, as expected. These examination findings were not observed in patients with ECI. The frequency of accompanying PMR was similar in all 3 groups.

When the laboratory findings were examined, no significant difference was found between the groups in terms of elevated ESR and CRP, leukocytosis, anemia and thrombocytosis.

Although the proportion of patients with a halo sign on temporal artery USG was low, all of these patients had CI. Two of these 3 patients underwent PET/CT, and both were negative in terms of vasculitic involvement.

Table 1. Demographic variables and clinical data of the study group

Demographic variables	
Age at diagnosis (years)	72.4±8.75
Female	13 (54.2)
Clinical findings	
Constitutional symptoms	11 (45.8)
Fever	2 (8.3)
Weight loss	7 (29.2)
Night sweats	2 (8.3)
Weakness	11 (45.8)
Headache	13 (54.2)
Jaw claudication	9 (37.5)
Visual loss	18 (75)
Tenderness on temporal artery	3 (12.5)
Temporal artery stiffness	2 (8.3)
Temporal pulselessness	7 (29.2)
PMR	6 (25)
Laboratory findings	
Sedimentation rate (mm/h)	72.64±25.48
C reactive protein (mg/L)	50.5 (19.2-128)
Total cholesterol (mg/dL)	204.3±46.7
LDL (mg/dL)	129.3±42.7
HDL (mg/dL)	44 (39.5-51.8)
Leukocytosis	7 (29.2)
Anemia	19 (79.2)
Thrombocytosis	8 (33.3)
Biopsy	
Temporal artery biopsy	14 (58.4)
Compatible	13 (54.2)
Incompatible	1 (4.2)
Biopsy from different area	1 (4.2)
Treatment	
Pulse steroid	11 (45.8)
Methotrexate	16 (66.7)
Azathioprine	2 (8.3)
Leflunomide	3 (12.5)
Tocilizumab	2 (8.3)

Values are given as n (%), median (IQR) or mean ± SD, HDL: High density lipoprotein, LDL: Low density lipoprotein, PMR: Polymyalgia rheumatica, SD: Standard deviation

Table 2. Comparison of the clinical data of the groups

	Cranial (n=18)	Extra-cranial (n=3)	Cranial and extra-cranial (n=3)
Demographic variables			
Age at diagnosis (years)	71.7±9.1	66 (61-66)	67 (62-67)
Symptom duration (months)	58.9±42.6	18 (6-18)	31 (1-31)
Symptom-diagnosis duration (months)	1 (0-4.25)	4 (4-4)	3 (0-3)
Female	9 (50)	2 (67)	2 (67)
Smoking	7 (39)	2 (67)	1 (33)
Clinical findings			
Constitutional symptoms	6 (33)	3 (100)	2 (67)
Fever	1 (6)	1 (33)	-
Weight loss	2 (11)	3 (100)	2 (67)
Night sweats	1 (6)	1 (33)	-
Weakness	6 (33)	3 (100)	2 (67)
Headache	10 (56)	1 (33)	2 (67)
Scalp tenderness	7 (39)	-	1 (33)
Jaw claudication	9 (50)	-	-
Visual loss	16 (89)	-	2 (67)
Tenderness or stiffness on temporal artery	9 (50)	-	-
Temporal pulselessness	5 (27)	-	2 (67)
PMR	3 (17)	1 (33)	2 (67)
Extremity claudication	-	-	1 (33)
Peripheral pulselessness	-	-	1 (33)
Tension difference between extremities	-	-	1 (33)
Murmur	-	1 (33)	1 (33)
Aneurysm in aortic branches	3 (16)	-	-
Diabetes mellitus	7 (39)	-	-
Hypertension	14 (78)	1 (33)	2 (67)
Coronary artery disease	7 (39)	-	-
Laboratory findings			
Erythrocyte sedimentation rate (mm/h)	69.4±24.5	88.3±27	61.7±31.5
C-reactive protein (mg/L)	46 (18.5-74)	133 (100-133)	20 (12-20)
Leukocytosis	6 (33)	1 (33)	-
Anemia	14 (78)	3 (100)	2 (67)
Thrombocytosis	6 (33.3)	1 (33)	1 (33)
Biopsy			
Compatible temporal artery biopsy	13/14 (92)	-	-
Biopsy from different area	-	1/1 (100)	-
Imaging			
Halo sign on temporal artery USG	3/11 (27)	0/1	0/3
Positive finding in PET/CT	0/7	3/3 (100)	2/2 (100)
Positive finding in cranial MR	5/8 (63)	1/1 (100)	1/1 (100)
Positive finding in MR angiography	0/3	1/2 (50)	1/2 (50)
Positive finding in CT angiography	0	0/1	0/1
Treatment			
Pulse steroid	10 (56)	0	1 (33)
Methotrexate	11 (61)	3 (100)	2 (67)
Azathioprine	1 (6)	0	1 (33)
Leflunomide	2 (11)	0	1 (33)
Tocilizumab	1 (6)	0	1 (33)
Acetylsalicylic acid	13 (72)	1 (33)	2 (67)
Anti-hyperlipidemic agent	3 (17)	1 (33)	1 (33)

Values are given as n (%), median (IQR) or mean ± SD, CT: Computed tomography, MR: Magnetic resonance, PET: Positron emission tomography, PMR: Polymyalgia rheumatica, SD: Standard deviation, USG: Ultrasonography

PET/CT was performed in 12 patients with a pre-diagnosis of GCA. The vasculitic involvement was found in all the 5 patients with ECI and CECI, while it was not observed in 7 patients with isolated CI. Although these data are meaningful, statistics could not be made due to the absence of PET/CT evidence in the CI group. Nine patients did not undergo CT or MR-angiography and PET/CT to evaluate large vessel involvement. All these patients were diagnosed with signs of CI. Only 1 of 12 patients who underwent PET/CT had PMR related musculoskeletal involvement. This patient also had vascular involvement. In addition, PET/CT was performed in 5 of 6 patients with PMR findings, one patient had PMR related musculoskeletal involvement. All patients received medium-high dose steroid therapy, 45.8% of them received pulse steroid (1 gram/day for three days). All patients who received pulse steroid therapy had CI with acute vision loss. All patients received conventional synthetic disease modifying anti-rheumatic drug therapy. 66.7% of them received methotrexate, 12.5% leflunomide, and 8.3% azathioprine as steroid sparing agent. Anti-interleukin-6 treatment was given to 2 patients (1 patient with CI and, 1 patient with CECI). 66.7% of the patients were taking acetylsalicylic acid and 20.8% were taking anti-hyperlipidemic treatment.

Discussion

GCA is a vasculitis that is among the large vessel vasculitides, but until recently, its cranial findings were better defined than its systemic involvement. With the widespread use of modern imaging techniques, ECI accompanying CI and isolated ECI have been better defined. Patients with isolated ECI often present with non-specific symptoms. While there may be localized ischemic manifestations, only systemic constitutional symptoms may be present.[3] When Schmidt et al.[8] compared GCA patients with CI and ECI, they found more constitutional symptoms and unclear inflammation in patients with ECI, while they reported more visual loss, headache, and temporal artery examination findings in the CI group. Also, the median time until the diagnosis was found to be longer in the ECI group. In our study, although it did not reach statistical significance (except for weight loss), constitutional symptoms were observed in all patients with ECI and this finding was more frequent in this group. As expected, loss of vision and pathological temporal artery examination was found more frequently in patients with CI. Muratore et al.[9] grouped patients as cranial GCA (C-GCA) and large vessel GCA (LV-GCA). LV-GCA group was younger than the C-GCA group, the duration of symptom-diagnosis period was longer, PMR symptoms and relapse rate were higher. In our study, symptom-disease duration and accompanying PMR were similar between the groups.

There was no specific laboratory test for the GCA. At least one of the acute phase values (CRP or ESR) is high in 96% of the TAB-positive GCA patients in the literature. Kermani et al.[10] also reported that acute phase values were higher in patients with accompanying PMR symptoms. Another study noted that sensitivity of the ESR and CRP together was 99% in TAB-positive GCA patients.[11] Czihal et al.[12] and Ghinoi et al.[13] found no significant difference between acute phase values in patients with CI and ECI. Considering the laboratory values of our patients, it was observed that the CRP value was higher in patients with ECI, but statistical significance could not be achieved. This was attributed to the small sample size and the wide range of CRP results.

Since the systemic symptoms and elevated acute phase reactants seen in elderly patients may often suggest an underlying malignancy, vasculitis can be diagnosed incidentally with imaging studies, especially with PET/CT. There are many studies in the literature evaluating the use of PET/CT in GCA. PET/CT seems to be a useful diagnostic modality for ECI, but not for CI.[14,15] Van der Geest et al.[14] recommends the use of PET/CT with TAB-negative patients or patients with isolated clinical PMR symptoms. Considerable progress has occurred in diagnostic imaging modalities since the GCA 1990 ACR diagnostic criteria were established.[7] This classification set excludes imaging methods. Recently, 2022 ACR/EULAR classification criteria for GCA were defined. Imaging findings that were missing in the previous classification set, such as the halo sign on temporal artery USG, involvement of axillary arteries, and FDG-PET activity in the aorta, were added to new classification criteria. This has increased the role of imaging modalities in the diagnosis of GCA.

The lack of objective clinical examination findings in ECI makes difficult the diagnosis. De Boysson et al.[16] evaluated the imaging findings of patients with cranial and extra-cranial GCA and found a more large vessel involvement in PET/CT scans in patients with ECI. Similar to the literature, while vasculitic involvement in PET/CT was observed in all patients with ECI and CECI, no PET/CT findings were observed in the isolated CI group in this study. Temporal artery USG has significant sensitivity and specificity in the diagnosis of GCA, particularly for patients with CI. Hypoechoic edematous wall swelling, also called a halo sign, is observed in those patients.[17] Temporal artery USG is an easily accessible method that can be performed in patients with cranial and visual symptoms. In our

study, temporal artery USG was performed in 62.5% of the patients, and a halo sign was detected in 20% of these patients. Recently, increased use and experience of USG by the rheumatologists will allow the evaluation of these patients in the symptomatic period.

The diagnosis can be made more easily with suggestive clinical findings in patients with CI. In addition, TAB provides the definitive diagnosis. TAB is the gold standard for GCA diagnosis by showing the typical histopathologic findings, namely, mononuclear cell infiltration of the artery wall.[18] Although stated as the gold standard, focal and segmental involvement of the vessel wall and technical pitfalls of the procedure make it difficult to confirm the diagnosis. However, the absence of suggestive clinical findings in ECI and the inability to determine the appropriate site for biopsy lead to diagnostic delay. Brack et al.[19] compared the TAB of the patients CI and ECI, they found a positivity rate of 100% and 42%, respectively. TAB findings were negative in 42% of patients with large-vessel GCA.

In some studies, TAB was also performed in patients without cranial findings and pathology results consistent with GCA were obtained.[20] This suggests that the disease has a systemic course even if it does not show any obvious symptoms. TAB was performed in 14 of 18 CI patients with visual findings, and diagnostic pathological findings were found in 92% of them. One patient presented with systemic symptoms and acute phase elevation, total abdominal hysterectomy and bilateral salpingo-oophorectomy performed with a suspicion of malignancy. The patient was diagnosed with GCA by pathological evaluation and PET/CT.

The shortcomings of our study are the small number of patients and the retrospective design. Due to the small number of patients in the groups, statistics could not be made. In addition, CT or MR angiography and PET/CT were not performed in 9 patients. If those patients had undergone these imaging modalities, accompanying ECI could have been detected.

Conclusion

As a conclusion, CI is common and diagnosed more easily due to its demonstrative clinical findings. ECI has begun to be defined better with the widespread use of imaging studies. ECI in GCA may present with different clinical findings, laboratory results, and may be defined as a different clinical entity as LV-GCA. The significant difference in terms of vasculitic involvement in PET/CT between C-GCA and LV-GCA is promising for the future studies in this regard.

Ethics

Ethics Committee Approval: The local ethics committee of Kocaeli University approved the study protocol (date: 13.09.2021, approval number: 2021/232).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.K., Ö.Ö.I., A.Y., A.Ç., Design: A.K., Ö.Ö.I., A.Y., A.Ç., Data Collection or Processing: A.K., Ö.Ö.I., A.Y., A.Ç., Analysis or Interpretation: A.K., Ö.Ö.I., A.Y., A.Ç., Literature Search: A.K., Ö.Ö.I., A.Y., A.Ç., Writing: A.K., Ö.Ö.I., A.Y., A.Ç.

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