Are Polymyalgia Rheumatica and Giant Cell Arteritis the Same Disease?

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Objective: To summarize the evidence about the relationship between polymyalgia rheumatica (PMR) and giant cell arteritis (GCA).

Methods: Review of relevant articles from the English-language literature.

Results: Epidemiologic studies suggest that PMR and GCA are closely related conditions affecting people over 50 years and frequently occurring in the same patient. PMR symptoms have been observed in 40 to 60 percent of GCA clinical series. Also, temporal artery biopsy may yield positive results for GCA in patients with isolated PMR. Conflicting HLA-DRB1 genotype results have been reported, and recent studies have shown that PMR and GCA have different expression of RANTES, TNFα microsatellite, and IL-6 promoter genetic polymorphisms. Search for a possible common infectious agent have yielded disappointing results. Although parvovirus B19 DNA is present in the artery wall of patients with GCA, this virus may be only an innocent bystander. Cytokine studies on a limited number of temporal artery biopsy specimens have shown that interferon-γ is produced in GCA and not in PMR, suggesting that this cytokine may be crucial to the development of overt vasculitis.

Conclusions: PMR and GCA frequently occur together but no definitive conclusions can be drawn about the nature of this association.

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INDEX WORDS: Polymyalgia rheumatica; giant cell arteritis; pathogenesis; relationship.
synovial structures is responsible for the typical symptoms (5,6). The histologic hallmark of PMR is mild synovitis in proximal joints and periarticular structures characterized by a predominance of macrophages and T cells, mostly CD4+ helper T cells (7).

GCA, which is less frequent than PMR, is a chronic vasculitis of the large and medium-size arteries. Although it may be widespread, symptomatic vessel inflammation usually involves the cranial branches of the arteries originating from the aortic arch (2). The most frequent and typical clinical manifestation is new onset headache and scalp tenderness related to inflammatory involvement of the temporal arteries. A marked inflammatory reaction with fever and other systemic symptoms and signs such as anorexia and weight loss is common (8). Other clinical features are related to ischemic manifestations caused by inflammatory vessel involvement. In approximately one third of the cases, neurologic manifestations such as ischemic events in the territory of the carotid or vertebrobasilar artery, or even mononeuropathies and peripheral polyneuropathies, are observed (9,10). A marked elevation of acute phase reactants reflects the systemic inflammatory reaction. In typical cases, physical examination shows tenderness, tortuosity, and nodularity of temporal arteries (2). When these findings are clinically detectable, duplex ultrasonography investi-

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<td><strong>PMR</strong></td>
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<td><strong>Frequency (in people older than 50 yrs)</strong></td>
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gation may confirm the presence of artery wall edema, stenosis, and reduced blood flow (11).

The typical histologic lesion is an inflammatory granulomatous infiltrate, with or without giant cells, usually located at the junction between the intima and the media, associated with marked disruption of the internal elastic lamina (12). Similar to PMR synovitis, the cellular infiltrates consist mainly of CD4+ T cells and macrophages (13).

Therefore, the only clinical characteristics shared by PMR and GCA are the marked elevation of acute phase reactants and the dramatic response to corticosteroids, although at different doses (2).

From a clinical point of view, the 2 disorders appear completely different, and PMR, especially when distal manifestations are present, is more similar to late onset rheumatoid arthritis (RA) than to vasculitis. On the other hand, when extracranial vascular features occur, GCA is more similar to Takayasu disease, differing only in the age of onset.

Several clinical studies support these statements. The occurrence of peripheral arthritis, particularly in both hands, may create some diagnostic difficulties between PMR and late onset RA. Patients with PMR may experience episodes of symmetrical arthritis which may lead to a diagnosis of RA (14). Furthermore, Healey noted patients who developed episodes of PMR and of seronegative RA at different times during follow-up, suggesting that PMR and late onset RA may be the same entity (15). In addition, 8% to 12% of patients with PMR develop periodic distal extremity swelling with pitting edema (6) and these patients would meet the American College of Rheumatology (ACR) criteria for RA (16).

In approximately 15% of the cases, the inflammatory process of GCA may affect the branches of the aortic arch, particularly the subclavian and axillary arteries, resulting in claudication of the arms and decreased pulses (17). Abdominal aorta and the lower extremities arteries may be involved as well (18). In these patients, the clinical picture, the imaging findings, and the histologic lesions (12) resemble those of Takayasu arteritis and only the age of the patient suggests the correct diagnosis.

Nevertheless, epidemiologic data suggest a possible relationship between PMR and GCA and many authorities consider them to be different phases of the same disease (19,20). In this article, we summarize the evidence related to a possible common genetic background, to a possible common triggering infectious agent, and to the possibility that vasculitis may represent a common pathogenetic mechanism.

METHODS

A systematic review of Medline database was performed to identify English-language articles related to the epidemiology, etiology, and pathogenesis of PMR and GCA. Articles were selected if they included both controlled and open studies on clinical series of patients who met the most commonly accepted criteria for the diagnosis of PMR (21-23), and of patients with positive temporal artery biopsy or who satisfied the ACR classification criteria for GCA (24).

RESULTS

Epidemiologic Data

PMR and GCA are closely related conditions affecting people over 50 years and frequently occurring in the same patient. The incidence of both diseases increases after the age of 50 and peaks between 70 and 80 years of age (25,26). The incidence of PMR appears relatively stable in recent years (27); in contrast, the incidence of GCA appears to have increased and autopsy studies suggest that GCA may be more common than clinically recognized (28). The 2 disorders have a very low prevalence rate in blacks, Hispanics, and Asian (29), and as shown by population-based studies, both PMR and GCA have an increased frequency at higher latitudes and in people with a strong Scandinavian ethnic background (26,27,30-34).

However, the low incidence rate of PMR and GCA in blacks probably should be revised upward in Americans of African ancestry (35). Indeed, in an 11-year retrospective study, Gonzalez et al found that in the Texas Gulf Coast PMR and biopsy-proven GCA were as frequent in blacks as in whites (36).

Regarding the North-South incidence gradient, reassessment is needed because of the following: 1) The incidence of PMR, and especially GCA, probably have been changing over time (3) and studies have not been performed during the same time period. 2) Depending on the countries or the regions within the same country, physicians may
be more or less aware of these conditions. Consequently, GCA and/or PMR may have been under-diagnosed, especially during the 1970s. Data from Israel support these concerns: the incidence of GCA/PMR reported by Friedman in the 60s was lower than in Europe (37), but was similar when the study was repeated in the 90s by Sonnenblick (38). The variation probably reflects better awareness of the disease over time among physicians. 3) Recognition depends on the methods of estimating the frequency and on the diagnostic criteria used. The prevalence of PMR and GCA have been assessed by 2 different methods: population-based studies derived from medical records and case-finding studies. The prevalence of PMR and GCA is much higher when estimated by case-finding methods (39). Regarding diagnostic criteria, they vary greatly among studies, most of which having been completed before the publication of ACR criteria. Furthermore, the diagnostic criteria for biopsy-negative GCA have been very strict in some but much looser in other studies. This problem is probably more important for PMR. The absence of validated classification/diagnostic criteria, and the lack of accurate diagnostic tests, may have negatively influenced the estimated prevalence in different countries. 4) Again, especially for PMR, different patient referral system in various countries may have contributed to incidence variations. 5) Some discrepancies also may be observed regarding the concurrence of the 2 diseases. PMR symptoms have been observed in 40 to 60 percent of GCA patients (23). PMR may begin before, simultaneously, or after GCA. Conversely, in PMR series the frequency of GCA varies between 0% to 80% (40). These latter results have been negatively influenced by the different methodological and diagnostic approaches. Population-based studies from several geographical areas have shown the presence of biopsy-proven GCA in 16 to 21 percent of patients with PMR (25,29). However, patients with PMR who do not have cranial symptoms and signs have a high probability of having normal findings on temporal artery biopsy.

Our experience confirms these data. PMR occurred in 42 of 92 (46%) patients with biopsy-proven GCA observed over a 5-year period (1996-2000) at Prato Hospital (unpublished data). PMR developed before GCA onset in 8 patients, simultaneously in 21 and after in 13. Conversely, we found that 12 of 76 (16%) consecutive patients satisfying the Healey criteria for the diagnosis of PMR had histologic evidence of GCA (41). However, only 1 (1.3%) of these patients did not have any clinical manifestations of GCA. Therefore, we only perform temporal artery biopsy in patients with cranial symptoms and/or signs. Alternatively, PMR patients without symptoms and signs of GCA may be investigated by duplex ultrasonography, but the sensitivity of this noninvasive diagnostic tool is limited (41).

**Evidence of Common/Different Common Genetic Background for PMR and GCA**

Epidemiologic studies have indicated that PMR and GCA may share a common genetic background in which multiple environmental factors play a pathogenetic role (3). Preliminary reports showed an association between HLA-DR4 and both PMR and GCA (42,43), but further studies indicated that DR4 was associated with PMR rather than GCA alone (44,45). Some European studies have reported conflicting results, and isolated PMR may have a different HLA class II genetic susceptibility that varies from 1 population to another (46-48). These discrepancies may reflect the different genetic background of the populations studied. The frequency of DR4 is higher in North European white populations. In Northern Italy, we observed the lowest frequency of DR4 in general population (16%), and no significant association of GCA/PMR with DR4 (49).

Subsequent studies of molecular typing found an increased frequency of DRB1*04 and HLA-DRB1*01 in patients with GCA and PMR (50-52), but this was not confirmed in other studies. In Northern Italy we did not find any association between these 2 alleles both for PMR and GCA (53). Recent Spanish studies indicate a different association with HLA-DRB1*01 and DRB1*04 for the 2 diseases, and isolated PMR was not associated with these alleles (54,55).

Genetic polymorphisms may be important factors in susceptibility to GCA and PMR and recent studies have observed some differences between the 2 conditions. One report noted an association between RANTES gene polymorphism and PMR, but not GCA (56). Both diseases shared a significant association with ICAM-1 gene polymorphisms in Italian patients (57) but not in individuals from Northwestern Spain (58,59). PMR and GCA are associated with different TNFα microsat-
ellite polymorphisms: the association of PMR with TNFβ3 and of GCA with TNFa2 seem to influence the susceptibility to these conditions independently of any HLA-DRB1 association (60). The same authors found that, in GCA patients, the expression of IL-6 promoter polymorphism at position 174 was associated with the development of PMR features, whereas this association was not found in isolated PMR, suggesting a different genetic susceptibility for the 2 diseases (61).

Evidence for Infection as a Trigger

A common infectious agent has been suspected but not confirmed for GCA and PMR. A close concurrence between the observed incidence peaks of PMR/GCA and epidemics of *Mycoplasma pneumoniae*, parvovirus B19, and *Chlamydia pneumoniae* has been observed (62,63). Moreover, an increased prevalence of antibodies to adenovirus, respiratory syncytial virus has been reported in PMR and GCA (64). However, most of these studies were performed on small series, usually not exceeding 20 to 30 cases, and did not reach a sufficient statistical power to prove the hypothesis.

Recent studies focused on the possible etiological role of human parainfluenza virus type 1 and parvovirus B19 both for PMR and GCA. In a case-control, multicenter study on 305 patients, French authors found a significant association between PMR and GCA and the IgM seroprevalence for human parainfluenza virus type 1 (65). A recent Spanish study on 85 patients with isolated PMR, 22 with GCA, and 36 with both PMR and GCA did not show any association with infection (66).

*Chlamidiae pneumoniae* has been detected by immunostaining and polymerase chain reaction (PCR) to be present in the artery wall of a small number of patients with biopsy positive GCA (67). Moreover, a significant association between histologic evidence of GCA and the presence of parvovirus B19 DNA in temporal artery specimens has been reported (68), and a previous epidemiological study from the Mayo Clinic showed a cyclic fluctuation of GCA incidence concurrent with cyclic infections of parvovirus B19 (26). However, a limited number of samples were examined, and little is known about the presence of parvovirus B19 DNA in age-matched healthy controls. Recently, Salvarani et al. did not find association between the presence of parvovirus B19 DNA in temporal artery biopsies and histological evidence of GCA (69). Also, Regan et al (71) failed to detect *chlamydia pneumoniae* in temporal artery biopsies of GCA patients by PCR (70). In addition, Danish investigators did not find evidence of DNA from parvovirus B19, *Chlamydia pneumoniae*, or human herpes virus in temporal artery biopsy specimens of GCA patients.

Is Vasculitis a Common Process in PMR and GCA?

Evidence for a common pathogenetic mechanism of vasculitis is provided by studies of cytokines in patients with GCA and PMR. In both diseases, increased plasma levels of circulating cytokines such as IL-6, IL-2, IL-1β, IL-1 receptor antagonist, vascular endothelial growth factor, platelet-derived growth factor, and monocyte chemoattractant protein 1 are detectable (72-78). In addition, in situ production of cytokines has been documented in the temporal arteries of patients with PMR who do not have histologic evidence of arteritis (79). The production of IL-1β and IL-2 and other T-cell and macrophage derived cytokines is shared by PMR and GCA, with the exception of IFNγ, which is present only in GCA. These findings suggest that subclinical vasculitis might be present in temporal arteries of patients with PMR and that IFNγ production may be crucial to the development of overt vasculitis (80). However, there is no good evidence that the musculoskeletal symptoms of PMR are related to vasculitis, and it does not clearly explain why only half of GCA patients develop PMR.

Recently, the vasculitis hypothesis for PMR was supported by studies using positron-emission tomography. An increased vascular uptake of 18F-glucose was detected in 54% and 56% of 13 patients with GCA and 12 with isolated PMR, suggesting an underlying vasculitis in PMR (81). However, despite negative temporal artery biopsy findings, half of the patients with isolated PMR had cranial signs and symptoms suggesting GCA. Therefore, a selection bias may have negatively influenced the results. This study is still in progress and the same authors presented an update not confirming the previous findings in PMR (82).

DISCUSSION

This review indicates that PMR and GCA frequently occur together for unclear reasons and no
definitive conclusions can be drawn regarding the nature of this association. Different methodologic and diagnostic approaches have negatively influenced the epidemiologic data relatively to incidence, racial and ethnic differences, and concurrence of the 2 disorders. Only population-based studies in different countries may clarify these concerns. To avoid patient selection bias, these studies should be adequately standardized regarding the classification/diagnostic criteria, the indications to perform temporal artery biopsy, the biopsy specimen size, and the histologic criteria. Relatively to the 2 latter items, the diagnostic accuracy of temporal artery biopsy is limited by the segmental distribution of the inflammation, and an adequate length of biopsy specimens of at least 3 cm with multiple sections is required (12,41). Moreover, pathologists should be aware that histological features of GCA may be somewhat atypical with respect to classic descriptions (83,84).

Reports indicating different genetic background for the 2 diseases are increasing but they should be confirmed on a greater number of patients. Moreover, the role of HLA alleles and genetic polymorphism associations in the susceptibility to PMR and GCA should be evaluated, taking into account their variable frequency in populations with different ethnic background (49).

There is no evidence for a common infectious agent for PMR and GCA. However, the sudden onset, seasonal distribution (85,86), and the prodromal flu-like symptoms described by some patients (87) have suggested an infectious cause. Studies designed to detect an increased prevalence of circulating IgG or IgM antibodies to various microorganisms yielded conflicting results and investigations on temporal artery biopsy specimens were inconclusive (69,70).

Although promising, cytokine studies on a larger number of patients are required to better address the vasculitis hypothesis for the 2 diseases. In particular, the role of IFNγ as a key regulator of inflammatory response both in PMR and GCA (80) needs to be confirmed.

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