Review

Environmental factors in polymyalgia rheumatica and giant cell arteritis

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ABSTRACT

Introduction. *Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are closely inter-related inflammatory conditions predominantly affecting individuals over 50 years of age. A significant geographic and demographic variability, with higher incidence rates in Caucasian patients of Northern European ancestry has been reported for both. Genetic predisposition, epigenetic alterations, immune system senescence, age-related changes of hypothalamic-pituitary-adrenal axis function, and environmental factors are theorised to influence disease susceptibility in PMR and GCA.*

Methods. *This narrative review synthesises the current evidence regarding environmental factors implicated in the pathogenesis of PMR and GCA. Relevant keywords, including "polymyalgia rheumatica", "giant cell arteritis", "environment", "gene-environment interaction", "precipitating factors" were used to search PubMed and Scopus databases.*

Results. *Immunogenic bacterial and viral infections with respiratory and neurotropic affinity, ultraviolet (UV) radiation, vitamin D deficiency, air pollution and cigarette smoking have been considered as trigger factors of PMR/GCA although with mixed results. Seasonal variations have been inconsistently linked to disease onset, with hypotheses ranging from infectious outbreaks in winter to UV-induced vascular inflammation in summer. Air pollution, particularly particulate matter (PM10), has been associated with increased GCA incidence, potentially through inflammatory amplification in predisposed individuals. Recent emerging evidence also implicates vaccines and immune checkpoint inhibitors as triggers for PMR and GCA-like syndromes, potentially through mechanisms of heightened immune activation.*

Conclusions. *The interplay between genetic and environmental factors, including possible epigenetic effects, highlights the complex immune pathophysiology of PMR and GCA. While some progress has been made in identifying triggers, many mechanisms remain unclear. Further research is necessary to elucidate causative pathways and early steps potentially informing preventive strategies.*

Introduction

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are closely related inflammatory diseases primarily affecting individuals over 50 years of age (1). PMR is characterised by bilateral pain and stiffness in the shoulders, cervical column, and pelvic girdle, often associated with systemic symptoms such as fatigue, weight loss, and fever (2, 3). GCA is the most common systemic vasculitis in adults and targets the medium and large arteries, manifesting with potentially severe complications including vision loss and aortic aneurysms (4, 5). Given the risk of imminent and irreversible visual loss, particularly in patients with concerning ischaemic symptoms such as transient visual loss or jaw claudication, diagnostic procedures should not delay the initiation of treatment in GCA (6).

These conditions often co-exist, as observational studies indicate that 40-60% of patients with GCA also experience PMR symptoms, while about 10-25% of individuals with PMR display clinical or imaging findings of GCA (7-9). This overlap supports the concept of a distinctive continuum recently

termed "GCA-PMR spectrum disease" (GPSD (10).

The incidence of PMR and GCA demonstrates striking geographical and demographic variability. Both conditions are significantly more common in Northern Europe, with Scandinavian populations reporting the highest incidence rates, while they are rare in Asian and African populations (11). The increased frequency among persons of Scandinavian ancestry, who reside in colder climate zones has led to claims of a possible role for vitamin D deficiency, at least in PMR due to UV deficiency (12, 13).

On the other hand, geographical distribution has prompted investigations into potential genetic predispositions, such as the HLA-DRB1*04 allele, a gene variant more commonly detected in northern and western Europe (14), alongside environmental triggers, including infections, environmental pollutants like particulate matter, stressful psycho-physical events, ultraviolet (UV) exposure and air pollution (15). Abnormal immune responses involving both the innate and adaptive systems, combined with age-related immune-endocrinological senescence and epigenetic modifications, may further contribute to disease susceptibility and the initiation of the pathophysiological process (16, 17).

Despite recent advances in understanding their clinical features and clues from treatment response to more targeted management with new biological immunosuppressants (18), the aetiology of PMR and GCA remains elusive. Evidence from the medical literature suggests a complex interplay of genetic and epigenetic influences, driven by potential exposures to endogenous and exogenous environmental triggers, and immune dysregulation (19, 20).

There is an emerging body of evidence regarding the role of environmental factors in rheumatic disease causation and exacerbation (21). This narrative review synthesizes the current evidence concerning the environmental factors associated with the onset of PMR and GCA, emphasising their potential roles in triggering or exacerbating these inflammatory diseases. Special attention is given to studies published within the past five years to provide an updated perspective on this evolving topic.

Methods

This narrative review synthesises the current evidence on environmental factors implicated in the pathogenesis of PMR and GCA. A comprehensive search of PubMed and Scopus databases was performed using relevant keywords, including "polymyalgia rheumatica", "giant cell arteritis", "environment", "gene-environment interaction" and "precipitating factors". While no date restrictions were applied to the database search to ensure an extensive review of the literature, particular emphasis was placed on studies published within the past five years to provide a focused update on recent advancements and emerging trends. Additionally, abstracts from the European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR) annual conferences from 2022 to 2024 were screened to capture the most up-to-date findings presented at major rheumatology meetings. Reference lists of included studies were also examined to identify additional relevant publications that may not have appeared in the initial database search**.** All relevant articles and abstracts were critically appraised, and their contributions to understanding the role of environmental factors in PMR and GCA were qualitatively synthesised.

Epidemiological patterns and geographical variability

PMR and GCA exhibit striking geographical and demographic differences in incidence and prevalence, which might be influenced by genetic and regional environmental conditions. These diseases primarily affect Caucasian populations and are especially prevalent in Northern Europe and North America (11).

Geographical distribution

Northern European countries report the highest incidences of PMR and GCA. In Scandinavia, incidence rates for PMR range between 34 and 113 per 100,000 individuals over the age of 50, and GCA incidence can reach up to 20 per 100,000 annually (22). Sweden and Norway, countries with predominantly Scandinavian ancestry, consistently report the highest prevalence and incidence of these conditions, while Finland, despite its Northern European location, has relatively lower GCA incidence rates (23), potentially due to its unique genetic makeup, as Finns are of Baltic rather than Scandinavian origin. Similarly, Olmsted County, Minnesota, where a high percentage of the population is of Scandinavian and other Northern European descent, reports incidence rates of 63.9 per 100,000 for PMR and up to 701 per 100,000 for prevalence (24).

In contrast, Southern European countries, such as Italy and Spain, as well as Oceania, report much lower incidence rates, with PMR cases ranging from 3.15 to 27.43 per 100,000, reflecting a trend of decreasing incidence in regions closer to the equator (11).

In Asian populations, such as those of Korea and Japan, the incidence of PMR and GCA is exceedingly rare, indicating either a lack of susceptibility genetic factors or potential protective genetic or environmental factors. A study from Saudi Arabia reported a small absolute number of positive biopsies over a 22-year period, suggesting a relatively low incidence of GCA in this Arab population (25). Robust epidemiological data on PMR and GCA are lacking for African populations, while data from Latin America countries such as in Argentina reveal an incidence and prevalence of these diseases closer to those of Northern European and North American populations, although there is considerable regional variation and more studies are needed to better understand the occurrence of these diseases in these populations (26) (Fig. 1).

Genetic predisposition and epigenetic influences

The geographic variability in PMR and GCA prevalence is closely linked to genetic factors (27). The HLA-DRB104 allele is strongly associated with GCA and PMR and is more prevalent in

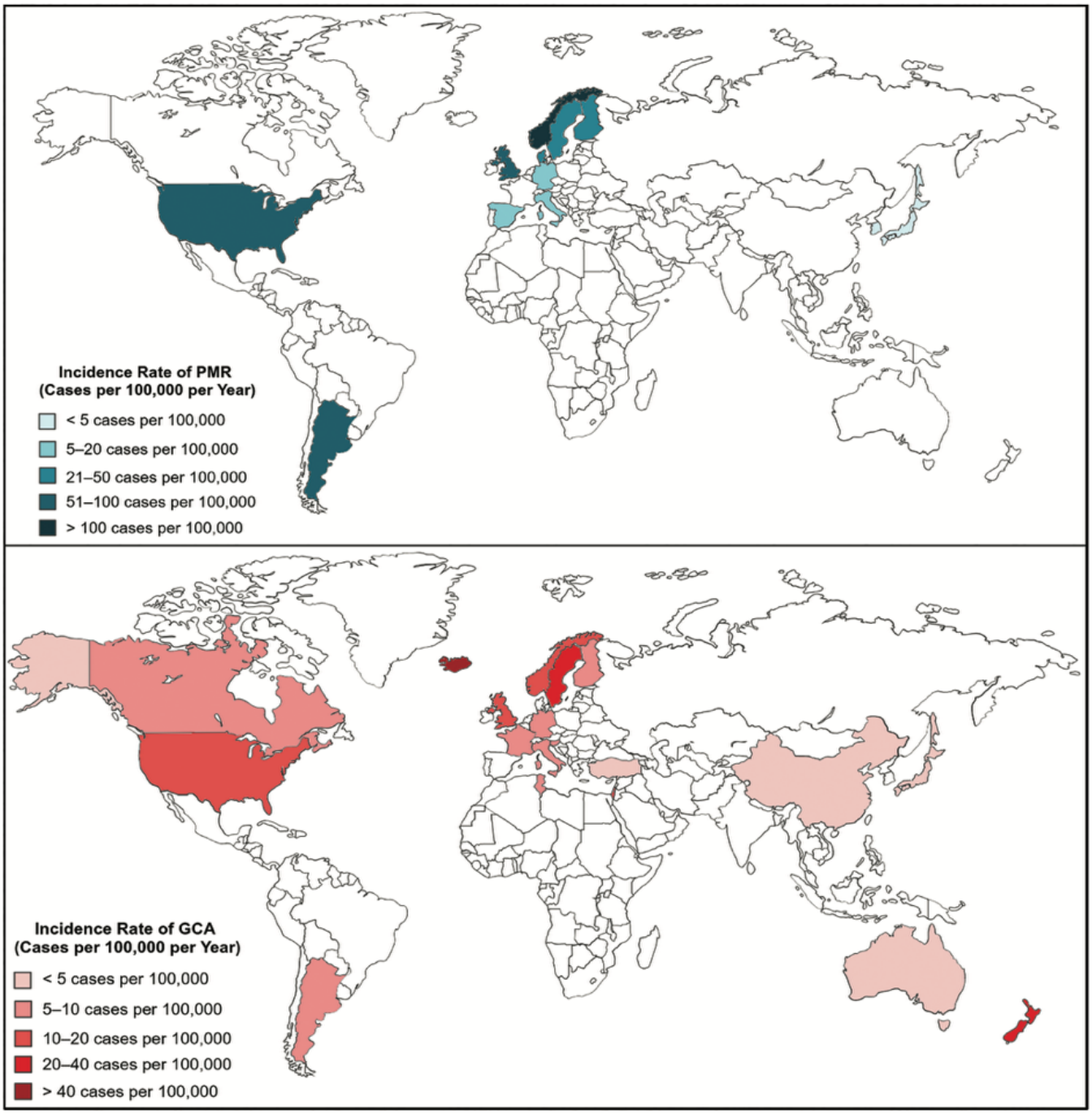

Fig. 1. An overview of worldwide incidence rates of polymyalgia (PMR) and giant cell arteritis (GCA). (Created with www.biorender.com, licenses TL-27NUW629 and RH27NUWATH).

Northern European populations (14). Genetic studies have highlighted the association of these HLA alleles with an abnormal immune response, possibly contributing to the development of inflammatory conditions such as PMR and GCA.

A meta-analysis demonstrated that the frequency of HLA-DRB104 alleles correlates with the latitude of the population studied, reinforcing a genetic basis for the North-South gradient in incidence rates (28). This allele encodes a specific variant of the HLA-DRβ1 molecule that plays a crucial role in antigen presentation to $CD4^+$ T cells. The presence of HLA-DRB104 may lead to the presentation of self-antigens or pathogen-derived antigens that mimic self, thereby triggering an aberrant immune response. This process results in the recruitment and activation of T cells and macrophages within the arterial wall and synovial tissues of peri-articular structures, leading to inflammation and tissue damage characteristic of GCA and PMR (29).

Additionally, polymorphisms in the protein tyrosine phosphatase non-receptor type 22 gene (PTPN22) involved in immune regulation have been associated with an increased risk of GCA. Variants in other genes related

to inflammatory pathways, such as tumour necrosis factor-alpha (TNF-α) and intercellular adhesion molecule-1 (ICAM-1), have also been implicated, suggesting broader genetic contributions to disease susceptibility beyond HLA alleles (27).

Moreover, genome-wide association studies (GWAS) have identified additional loci such as MFGE8, VTN, and CCDC25, implicating processes such as angiogenesis and neutrophil extracellular traps (NETs) in GCA susceptibility (30). These findings support the notion that both genetic susceptibility and inflammatory cascades involving endothelial and immune cell interactions might drive the disease.

Epigenetic mechanisms provide further strong evidence towards understanding of disease variability and treatment responses. DNA methylation studies in $CD14^+$ monocytes from patients with GCA revealed global hypermethylation patterns. Differential methylation at key sites, such as ITGA7 and CD63, aligns with dysregulated gene expression, contributing to monocyte activation, vascular remodelling, and glucocorticoid response pathways (31). A genome-wide methylation study of inflamed arterial tissue from patients with GCA presented at the 2024 EULAR conference identified over 200,000 hyper- and hypomethylated CpG sites (32). Functional annotation revealed strong connections to immune pathways, including myeloid cell differentiation and $CD4^+$ T-cell regulation, as well as structural pathways such as extracellular matrix organisation and angiogenesis.

In PMR, exome sequencing has linked deleterious rare variants in inflammasome-related genes like NLRP12, PLCG2, and NLRP3 to its pathogenesis, reinforcing the overlap with autoinflammatory pathways (33). These rare alleles increase susceptibility by modulating inflammasome activation central to cytokine release and systemic inflammation. Gene expression profiling in PMR has identified dysregulated transcripts associated with inflammation and extracellular matrix remodelling in muscle tissues. Increased expression of IL-6, a pivotal pro-inflammatory cytokine, underscores its critical role in PMR, while prednisolone effectively suppresses these inflammatory signatures (34).

Epigenetic influences in GCA extend beyond DNA methylation, with microRNA (miRNA) dysregulation emerging as another critical layer of complexity. Pro-inflammatory miRNAs, such as miR-132, miR-155, miR-146a, and miR-146b, are significantly upregulated in inflamed temporal arteries, promoting vascular inflammation through pathways involving T-cell and macrophage activity, as well as ICAM-1 expression (31-34). Conversely, regulatory miRNAs, including the miR-30 family, are under-expressed, contributing to aberrant immune responses via dysregulation of the calcineurin/NFAT signalling pathway. While these findings shed light on the pathogenesis of GCA, data on miRNA involvement in PMR remain scarce and warrant further investigation (35-38).

Results of these and related studies suggest that ongoing and future approaches incorporating integration of multi-omics datasets and functional studies hold promise for identifying novel therapeutic targets and biomarkers predictive of disease susceptibility and treatment response (39).

Epidemiological trends

Epidemiological studies on PMR and GCA reveal complex trends in disease occurrence over time. Early population based long-term longitudinal studies such as those from Olmsted County, Minnesota, suggested a gradual rise in age- and sex-adjusted incidence rates of GCA over the first 30 years of 50-year observation period, attributed mainly to improved diagnostic capabilities, aging populations in Western countries, and greater disease awareness among healthcare providers (40). Similarly, rises in PMR incidences were shown in a UK-based study detecting an increase from 6.9 to 9.3 per 10,000 person-years between 1990 and 2001, potentially reflecting changes in diagnostic practices rather than true prevalence increases (41).

In contrast, more recent subsequent studies have provided mixed evidence about whether these conditions are in fact becoming more common. For example, a UK-based study reported a stable PMR incidence rate of 95.9 per 100,000 person-years among individuals aged 50 and above, with no significant upward trend over time (42). As well, data from Olmsted County for the period 2000–2014 also affirmed no significant increase in PMR incidence, with factors such as age and female sex remaining stronger predictors rather than calendar year (24, 43). Another US-based study showed that the prevalence rates of GCA and PMR in 2015 were similar to previously published prevalence estimates in the late 1990s (44).

Overall, while some early evidence indicated a potential rise in PMR and GCA diagnoses, more recent analyses suggest that these trends in incidence may largely reflect evolving diagnostic practices and demographic shifts rather than true increases in disease burden. At the same time, as the global population ages, the absolute number of PMR and GCA cases is expected to rise, given their higher occurrence in older individuals (45). This increase in prevalence reflects the increasing number of older individuals who are more susceptible to these diseases, rather than a change in individual risk. The need for continued epidemiological monitoring across diverse populations and geographies remains critical to understanding the dynamics of these conditions.

Environmental triggers and seasonal pattern

Environmental factors, including those that may potentially fluctuate with seasonal variations, infections, ultraviolet (UV) radiation exposure, and air pollution, have been long suspected of contributing to risk for developing PMR and GCA (Fig. 2) (46, 47). While these factors are not universally established as definitive triggers, they might provide some clues into the multifactorial nature of these diseases.

Infections as triggers

The nature of the acute clinical presentation of PMR and GCA, accompa-

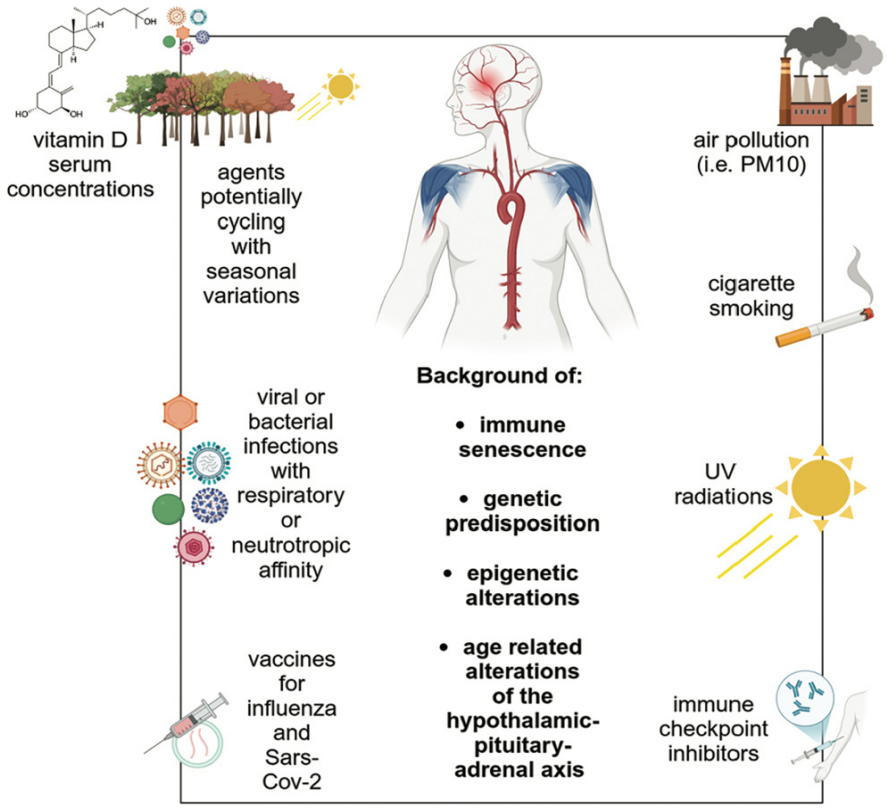

Fig. 2. Environmental triggers investigated in observational studies for polymyalgia and giant cell arteritis (created with www.biorender.com, license DF27NUYAQF).
PM10: particulate matter 10 micrometers or less in diameter; Sars-Cov-2: severe acute respiratory syndrome COronaVirus 2; UV: ultraviolet.

nied by systemic symptoms such as fever and malaise, has long been cited as supporting for the hypothesis that infections may trigger these diseases. Epidemiological studies have suggested associations between seasonal outbreaks of respiratory infections and peaks in PMR and GCA incidence (48). *Mycoplasma pneumoniae* (49), *Chlamydophila pneumoniae* and *parvovirus B19* (50) have been linked with increased cases of GCA and PMR, particularly during epidemic cycles. These infections may initiate an aberrant immune response in genetically predisposed individuals, although case-control seroprevalence studies have not consistently confirmed this association (51-53).

Viral infections, particularly *human parainfluenza virus type 1 (HPIV-1),* have also been proposed as possible triggers. Previous reports have shown higher anti-HPIV-1 IgM prevalence in patients with newly diagnosed GCA and PMR compared to controls, suggesting a potential association with disease onset (51). These findings are consistent with the detection of seasonal IgM seroprevalence peaks aligning with the seasonal variations of these diseases reported in some observational studies (54). Nevertheless, evidence for infectious triggers remains inconclusive, as other studies have found no associations between infections such as parvovirus B19, *Chlamydia pneumoniae*, respiratory syncytial virus, measles virus, herpes simplex viruses 1 and 2, Epstein-Barr virus, or human herpesvirus and the onset of PMR/GCA within a few months of exposure (55).

Herpetic infections, particularly *varicella zoster virus* (VZV), have gained significant attention as potential triggers for GCA. VZV DNA and antigens have been detected in temporal artery biopsies of both histologically positive and clinically suspected GCA cases, particularly in "skip lesions" along the adventitia (56, 57). It may be that viral DNA detected in arterial lesions of patients with GCA likely reflects immune responses to latent pathogens rather than being a proof of direct causation (56). A carefully done population based, longitudinal evaluation of GCA incidence failed to provide evidence of a causative role for VZV, although a more recent meta-analysis showed an increased risk of GCA following prior herpes zoster infection, particularly when infections occurred within a year of diagnosis (58, 59).

In addition to VZV, other viral agents have been identified in temporal artery specimens of GCA patients. A study using real-time quantitative polymerase chain reaction found that parvovirus B19 DNA was present in 54% of temporal artery biopsies from patients with histologically confirmed GCA, compared to 38% of controls (60). The viral load was significantly higher in GCA patients, suggesting that B19 may contribute to disease pathogenesis, particularly in cases with high viral burden. In contrast, no significant differences were observed for VZV and HHV-6 DNA prevalence or viral load between GCA patients and controls (60).

More recently, during the COronaVIrus Disease 19 (COVID-19) pandemics, some studies have described patients presenting with musculoskeletal symptoms consistent with PMR following Sars-Cov-2 infection(61, 62). In a large multicentre study including 267 cases of inflammatory rheumatic diseases with onset following Severe Acute Respiratory Syndrome COronaVirus 2 (SARS-CoV-2 infection), 21.3% of patients were classified as having PMR, defined clinically by the examining rheumatologist (63).

Several case series and narrative reviews have discussed PMR-like syndromes post-COVID-19, suggesting that the infection may act as a trigger in predisposed individuals (*e.g.*, older adults) or simply exacerbating a pre-existing subclinical disease (64). However, it remains unclear whether these syndromes are identical to classic PMR, as they share similar clinical and laboratory findings but may differ in aspects such as patient demographics, with younger individuals sometimes being affected post-COVID-19 infection (65). The relationship between the infectious triggers and the onset of these diseases

is complex and might be likely influenced by genetic susceptibility, immune senescence and age-related dysfunction of the hypothalamic-pituitary-adrenal axis (19, 66).

Ultraviolet (UV) light exposure and circadian rhythms

The role of UV radiation in PMR and GCA pathogenesis continues to be debated. Older studies suggested that UV-induced damage to the internal elastic lamina of superficial arteries could act as an antigenic trigger, especially in light-skinned individuals with high skin sensitivity, such as those of Nordic descent. This mechanism aligns with the histopathological similarities between actinic granulomas and the vascular lesions of GCA (67). Additionally, UV radiation can reactivate latent viruses, providing another potential pathway for its involvement. Somewhat relatedly, a study of solar flare cycles, which have stronger effects away from the equator, suggested an increase in occurrence of GCA and rheumatoid arthritis following flare bursts (68).

More recent research has found little evidence to support a direct link between sun exposure and increased PMR or GCA risk. A recent large prospective cohort study in Sweden, for example, found no protective or harmful effect of active sun exposure on PMR or GCA development (69). This finding suggests that UV radiation alone is unlikely to be a significant environmental trigger. Interestingly, regions with high UV exposure, such as southern Europe, often report lower incidences of these conditions, further complicating the narrative (70).

Vitamin D deficiency is more common in North geographical areas and has been associated with PMR due to UV light deficiency (12). Indeed, a body of evidence suggests that vitamin D, as a secosteroid hormone, may exert a protective role on muscle health not only in terms of muscle regeneration and mitochondrial health but also by exhibiting anti-inflammatory properties (71, 72).

Finally, the circadian alternation of day and night (UV rhythms) may contribute to the circadian pattern of PMR clinical manifestations (*e.g.*, morning pain and stiffness) through mechanisms similar to those in rheumatoid arthritis (73, 74). The nighttime rise in melatonin and decrease in cortisol could further explain the nocturnal inflammation and morning symptoms(75). These circadian rhythms in PMR are also taken into account in optimizing glucocorticoid treatment, with night administration (*e.g.*, using modified-release prednisone formulations) being an option for patients experiencing significant morning stiffness from this chronic condition (76, 77).

Seasonal patterns

Seasonal variations in PMR and GCA incidence have been widely studied, with conflicting results. Some data indicate higher incidences of the diseases during summer months (78-81), while others suggest peaks in winter (82, 83). Studies reporting seasonal variations in PMR and GCA have proposed various speculative theories to explain this observation. Peaks in winter were often linked to seasonal respiratory infections, while higher incidences in summer were attributed to actinic (UV) damage, potentially triggering antigen exposure and initiating an inflammatory response by the affected superficial arteries and synovial tissues.

A potential contributor to the seasonal variation in PMR and GCA may be hypovitaminosis D, as vitamin D serum concentrations are known to fluctuate with the seasons and are influenced by the latitude gradient, and indeed, recent studies have reported the influence of seasonal vitamin D variations on clinical manifestations in rheumatoid arthritis and systemic sclerosis (84). Vitamin D deficiency has been linked to increased susceptibility to other immune-mediated rheumatic diseases, including inflammatory conditions such as PMR and GCA (85). Lower levels of vitamin D in winter months, particularly in regions with lower sunlight exposure, might contribute to the onset or exacerbation of these diseases (12). However, the role of vitamin D in this context remains speculative, and further studies are needed to determine whether hypovitaminosis D could play a role in the onset of PMR and GCA.

Contrary to studies suggesting seasonal trends, other investigations have failed to find a significant association between seasonal onset and PMR or GCA (86, 87). These inconsistent results may be attributed to the heterogeneity of study designs, variations in classification criteria, differences in defining the precise onset of symptoms and the influence of undetermined confounding variables. In this regard, a recent systematic review and meta-analysis of 22 studies did not show any significant seasonal clustering in the onset of PMR and GCA, potentially suggesting that the environmental factors triggering the diseases might not follow a seasonal pattern (88). Ultimately, the potential lack of seasonal clustering may suggest that environmental triggers for these diseases operate independently of seasonality, or that a combination of genetic and environmental factors might mask any potential seasonal effect.

Air pollution and particulate matter

Emerging evidence highlights the potential role of air pollution, particularly exposure to fine particulate matter (PM10), in triggering GCA. A recent study identified a strong association between elevated PM10 levels and increased GCA incidence, particularly in regions with high pollution, such as the Po Valley in Northern Italy (89). For every 10 $\mu g/m^3$ increase in PM10 concentration over a 60-day period, the study found a 27% rise in GCA incidence, emphasizing the inflammatory potential of air pollution.

Particulate matter may act as a non-specific inflammatory stimulus, amplifying immune responses in genetically predisposed individuals. This mechanism is particularly relevant in older adults, who may already exhibit immune senescence and chronic low-grade inflammation. Interestingly, the association between air pollution and GCA was stronger in non-smokers, suggesting that air pollution may play an independent role rather than synergistically interacting with other inflammatory exposures such as smoking. Because smoking itself is a risk factor for

the development of systemic rheumatic diseases including GCA, it is possible that the effect of air pollution exposure was overshadowed by smoking (90).

While direct evidence for a link between air pollution and PMR is more limited, a large cohort study from Quebec, Canada, found that higher exposure to fine particulate matter (PM2.5) was associated with a 12% increase in the incidence of systemic autoimmune rheumatic diseases, including PMR(91). These findings suggest that air pollution may also contribute to PMR onset, acting as a general inflammatory stimulus in predisposed individuals. However, further studies are needed to confirm this association and delineate its specific impact on PMR.

The role of vaccines in PMR and GCA onset

PMR and GCA have occasionally been reported as rare adverse events following vaccinations, including influenza and COVID-19 vaccines. A study analysing 358 patients with GCA and PMR identified 10 cases (2.8%) linked to influenza vaccination, with these cases showing a higher likelihood of carrying the HLA-DRB1*13:01 haplotype, suggesting a genetic predisposition (92). Notably, most post-influenza vaccination PMR/GCA cases were self-limiting. Case reports have also documented PMR relapses after adjuvanted influenza vaccines in previously diagnosed patients (93).

Similarly, there have been reports of PMR-like syndromes following COVID-19 vaccination. For example, a case series described four patients developing PMR symptoms within 1-2 weeks after receiving the AstraZeneca or Pfizer vaccines. These patients exhibited elevated inflammatory markers and responded well to glucocorticoids (94). A retrospective analysis suggested no significant differences in disease course or treatment response at 6 and 12 months between PMR following mRNA COVID-19 vaccination and primary PMR, indicating that vaccine-associated PMR might not represent a distinct entity (95). Similarly, GCA cases following COVID-19 vaccination have shown good responses to standard treatments, such as high-dose glucocorticoids and tocilizumab, with outcomes comparable to primary GCA cases (96).

A global pharmacovigilance study using World Health Organization (WHO) database data identified 147 cases of GCA and 290 cases of PMR following COVID-19 vaccination. The median time to symptom onset was 4-6 days post-vaccination. Interestingly, the reported odds ratios for GCA and PMR were lower for COVID-19 vaccines compared to influenza vaccines (0.5 and 0.2, respectively), suggesting a relatively lower risk with COVID-19 vaccines (97).

A proposed mechanism for these rare events is the Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA), whereby vaccine adjuvants may trigger autoimmune responses in genetically predisposed individuals (98). While the concept of ASIA remains controversial, it underscores the potential role of individual susceptibilities in these occurrences.

Most of these rare adverse events are self-limiting and manageable. It is crucial to emphasise that the benefits of vaccinations, including the prevention of severe infectious diseases, far outweigh the potential risks of such uncommon reactions.

Immune checkpoint inhibitors and PMR/GCA-like syndromes

Immune checkpoint inhibitors (ICIs) are a cornerstone in cancer immunotherapy. They have been implicated in the development of immune-related adverse events (irAEs) including PMR-like syndromes of. These drugs, including PD-1 inhibitors (*e.g.*, pembrolizumab) and CTLA-4 inhibitors (*e.g.*, ipilimumab), work by enhancing T-cell activation to attack cancer cells. However, this heightened immune activation can lead to off-target inflammation, resulting in autoimmune-like conditions. PMR-like syndromes induced by ICIs (ICI-PMR) have been reported, often presenting with proximal muscle stiffness, pain, and elevated inflammatory markers similar to classical PMR (99-101).

A recent systematic literature review highlighted distinct features of ICI-PMR and ICI-GCA compared to their idiopathic counterparts (102). Among ICI recipients, the estimated prevalence was 0.1% for ICI-PMR and 0.06% for ICI-GCA. ICI-PMR occurred predominantly in males (male-to-female ratio 1.7:1) with a mean age of 71 years, while ICI-GCA showed equal sex distribution with a similar mean age. Both were most commonly associated with PD-1/PD-L1 inhibitors. ICI-PMR presented with inflammatory pain in the girdles (100%), though pelvic girdle involvement was inconsistently reported, and peripheral arthritis occurred in 35% of cases. Inflammatory markers were normal or mildly elevated in 26% of patients with ICI-PMR. Individuals with ICI-GCA often manifested with cephalic symptoms (75%), large-vessel involvement (54%), and permanent visual loss (23%). Both conditions responded well to glucocorticoids, with remission rates of 84% in ICI-PMR and 96% in ICI-GCA, though relapses occurred in 14% and 17%, respectively, and some cases required additional immunosuppressive treatment (102).

These findings emphasise the need for vigilant monitoring during ICI therapy and highlight the distinct clinical profiles of ICI-induced rheumatic syndromes. Early recognition and tailored management are essential to optimise cancer treatment outcomes while minimising the impact of irAEs.

Conclusion

PMR and GCA represent a continuum of inflammatory diseases influenced by a complex interplay of genetic predisposition, environmental triggers, and immune dysregulation. Geographical variability, linked to genetic factors such as the HLA-DRB1*04 allele, highlights the interplay between genetic and environmental influences, through epigenetic mechanisms. Infections, ultraviolet radiation and vitamin D (secosteroid D) deficiency, air pollution, cigarette smoking and other potential factors have been proposed as triggers or risk factors, but evidence remains partially inconclusive for most. Post-vaccination cases of PMR and GCA appear to have clinical outcomes

comparable to primary forms of these diseases, whereas immune checkpoint inhibitor-induced syndromes may exhibit distinct or milder presentations.

Advances in genetic and epigenetic research will continue to deepen our understanding of disease mechanisms. There is a crucial need for further studies to refine prevention and treatment approaches based upon improved knowledge of factors associated with disease risk and exacerbation. Further studies of environmental factors, epidemiological patterns across different countries and regions of the world, and the interplay between genetic predisposition and external triggers might be important to refine preventive strategies for these, and other systemic rheumatic diseases.

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