GCA is a large vessel vasculitis of unknown aetiology characterized by the presence of giant cells in biopsy specimens from large arteries. GCA shows a striking age tropism with a marked increase in incidence with age over 50 years. GCA is classified using the ACR criteria, developed in 1990 [1].

Prospective studies from Scandinavia report annual incidence figures for biopsy-proven GCA of 15–35 per 100 000 individuals aged over 50 years [2], similar rates have been reported from Olmsted County (Minnesota, USA) and in a UK community based study (reviewed in [2]). The incidence increases with age, peaking aged 80 years or older; very few cases occur aged less than 50 years. Most series from Northern Europe report a greater incidence in women, with a female to male ratio of around 2.5:1; the female excess is lower in southern European countries and Israel whilst in Northwest Spain, India and Turkey the ratio is equal.

In Olmsted County between 1950–54 and 1980–84 there was an increase from 6.7/100 000 to 28.5/100 000 in persons aged >50 years. The rate then stabilized and has not risen further. A similar increase in incidence has been documented in Göteborg, Sweden between 1976 and 1995 from 16.8/100 000 to 30.1/100 000 persons aged >50 years. GCA appears to be more common in Caucasian populations compared with non-Caucasians, however, there are few studies directly comparing different populations [2]. The incidence is highest in Scandinavians and in populations descended from them. The Viking heritage of the UK might be responsible for the relatively high frequency of GCA seen in the UKGPRD study; the incidence is highest in a region with marked Viking ancestry [3]. GCA is much less common in southern European populations, which have a different genetic background [4]. The Olmsted county population is descended from Scandinavian migrants to the USA. Studies from Tennesee and Texas have reported a much lower incidence in African-Americans and Hispanics. There is a low prevalence in Japan compared with Europe [5].

The epidemiology of a rare disease such as GCA poses challenges to epidemiologists. One difficulty is case definition. The ACR (1990) criteria for GCA are sensitive and specific and have been in use in most recent studies. The age criterion (age >50 years) means that patients presenting with a large vessel vasculitis below 50 years of age are often considered not to have GCA. The ACR did not mandate a biopsy. Many studies have been hospital based and only include biopsy proven cases. Many cases are managed solely in the community without a biopsy leading to uncertainty as to the veracity of the diagnosis. The UKGPRD study only validated a small sample (50) of cases of which only five had a biopsy and two were positive [3]. Novel techniques for diagnosis such as temporal artery ultrasound, large vessel angiography of FDG-PET imaging are not considered in the current classification schemes.

A further difficulty is case capture. GCA is rare, occurs in the elderly and therefore a large elderly population is required to determine the incidence and prevalence, and this poses questions of feasibility. A larger population increases the risk of incomplete case detection but permits a reasonable number of cases to be collected in a practicable time frame; whereas a smaller population requires a much longer time frame to collect the necessary cases, which also may not be feasible. Statistical methods of capture-recapture enable estimates to be made of the number of missing cases.

The existing literature on the epidemiology of GCA contains a number of deficiencies. Many of the existing studies only report biopsy positive cases and this leads to an underestimate of the number of cases. The biopsy rate varies between centres. The histological detection of vasculitis is dependent on an adequate length specimen and examination of several sections. Furthermore skip lesions occur and the detection of vasculitis is dependent on an adequate length specimen. The biopsy rate varies between centres. The histological examination of several sections. Furthermore skip lesions occur. A number were considered not to have GCA. The ACR did not mandate a biopsy. Many studies have been hospital based and only include biopsy proven cases. Many cases are managed solely in the community without a biopsy leading to uncertainty as to the veracity of the diagnosis. The UKGPRD study only validated a small sample (50) of cases of which only five had a biopsy and two were positive [3]. Novel techniques for diagnosis such as temporal artery ultrasound, large vessel angiography of FDG-PET imaging are not considered in the current classification schemes.

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Therefore an urgent need for a large-scale prospective community based study with robust methods of diagnosis and classification, and appropriate statistical power.

References

3. PATHOGENESIS OF GIANT CELL ARTERITIS

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GCA is an immune-mediated chronic inflammatory disease of large vessels. The pathogenesis of GCA is poorly understood. The epidemiology of GCA strongly indicates that genetic background, ageing and gender undoubtedly play a role. Various polymorphisms have been associated with increased risk of GCA but the strongest association appears to be with variants in the class II major histocompatibility complex reinforcing the concept that GCA is an immune-mediated disease [1]. However, the role of the putative susceptibility gene(s) has not been identified. Activated dendritic cells are present in lesions and are thought to play an important role in T-cell activation [2, 3]. GCA is characterized by a prominent Th1-mediated immune response with vigorous expression of IFNγ and IFNβ induced products in lesions in accordance with the granulomatous nature of lesions [2, 3]. In recent years it has become apparent that a Th17-mediated immune response also contributes to GCA and that patient with prominent Th17 response respond better to glucocorticoid treatment [4, 5].

Amplification cascades following these initiating events are seminal in the development and perpetuation of GCA lesions. IFNγ is a potent activator of macrophages which maintain inflammatory cascades and participate in vascular injury. Macrophages produce pro-inflammatory cytokines IL-1, TNFα and IL-6 among many others which correlate with the intensity of the systemic inflammatory response, typical of the disease [6]. Tissue expression and serum concentrations of TNFα and IL-6 correlate with disease persistence [6]. Chemokines, endothelial adhesion molecules and colony-stimulating factors are also produced in lesions and reinforce inflammatory loops by recruiting and expanding the half-life of additional inflammatory cells [6, 7]. Angiogenic factors are produced in lesions and promote neovascularization providing new entries for infiltrating leucocytes [8].

Activated macrophages produce reactive oxygen species which contribute to oxidative damage and vessel wall injury [9]. Matrix metalloprotease (MMP-9 and MMP-2) expression, activation and proteolytic activity have been detected in lesions and, given their elastic fibres and abnormal vascular remodelling [10].

Currently the treatment of GCA mainly relies on glucocorticoids with induce a rapid relief of symptoms but are unable to induce sustained remission in 60–70% of patients. Understanding the pathogenic mechanisms leading to GCA may lead to the identification of better therapeutic agents. The association between increased expression of TNFα and persistent disease activity provided support to the performance of clinical trials blocking TNF with infliximab, etanercept or adalimumab which, unfortunately, have proved insufficient to abrogate disease activity and maintain remission, presumably due to redundancy in inflammatory pathways [11, 12]. Currently, blocking the IL-6 receptor with tocilizumab is being tested in an international multicentre trial. IL-6 is a multifunctional cytokine involved not only in inducing the acute phase response and ensuing systemic symptoms but also in maintaining the Th17 pathway. Interfering with CD28-mediated T-cell co-stimulation with abatacept, presumably dampening antigen presentation, is also currently being tested in a multicentre trial.

Growth factors produced by activated macrophages or by injured vascular smooth muscle cells drive a vascular remodelling programme leading to myofibroblast differentiation of vascular smooth muscle cells, migration towards the intimal layer and deposition of extra cellular matrix proteins. This leads to intimal hyperplasia and vessel occlusion, source of the ischaemic complications of GCA patients. Several factors including PDGFs, TGFβ and endothelin-1, may contribute to myofibroblast activation and production of matrix, eventually leading...
to vascular occlusion [13, 14]. Their expression in lesions is not downregulated by glucocorticoids suggesting that mechanisms of vessel occlusion may require a specific approach in large- vessel vasculitides [15, 16].

References


GIANT CELL ARTERITIS

4. GENETICS OF GCA: GWAS

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GCA is considered a complex disease with a poorly known genetic component. Genetic studies in GCA clearly point to the role of genes located in the MHC region being strongly associated with GCA. Moreover, recent studies have indicated that other key markers of the immune and inflammatory response are crucial players in the development and progression of GCA.

In particular, we have recently identified NLRP1 and PTPN22 as novel GCA susceptibility genes, among other pieces of the genetic puzzle underlying the pathogenesis of this complex disease. An important step forward has been made in recent years towards the understanding of the genetic basis of immune-mediated diseases through the use of high-throughput genotyping platforms such as genome-wide association study (GWAS) and the Immunochip custom SNP array. At present, we are applying these new technologies—GWAS and IChip—to the identification of novel genetic factors involved in GCA.

5. BIOMARKERS IN PMR, GCA AND OTHER LARGE VESSEL ARTERITIDES

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Introduction: Chen et al. [1] state that biomarkers can be classified into five categories based on their application in different disease stages: antecedent biomarkers to identify the risk of developing an illness; screening biomarkers to screen for subclinical disease; diagnostic biomarkers to recognize overt disease; staging biomarkers to categorize disease severity, and prognostic biomarkers to predict future disease course, including recurrence, response to therapy, and monitoring efficacy of therapy. Interestingly an expert at the National Institutes of Health (NIH) has defined a biomarker as ‘a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention’ [2]. According to this definition, biomarkers include not only laboratory tests but also function testing, electrocardiographic testing and imaging depending on the underlying disease. The clinical value of biomarkers has to be studied in prospective clinical trials with standardized treatment and clear outcome parameters and depends on their sensitivity/specificity and reliability. Also many biomarkers have both prognostic and predictive features. Here we summarize the use of biomarkers in PMR, GCA and other large vessel vasculitides including Takayasu arteritis (TA), isolated aortitis (as a single organ vasculitis) and Behçet’s disease (BD, as a variable vessel vasculitis).

Methods: Currently available international diagnostic and classification criteria were screened for the recommended use of laboratory and imaging biomarkers. For PMR, preliminary results from the ongoing EULAR/ACR project for the assessment of management recommendations (under the guidance of B Dasgupta and E Matteson) and data from a review on remission and relapse of the diseases are summarized [3].

Results: Besides ESR and CRP, no validated laboratory biomarkers have been established for PMR, GCA and other large vessel arteritides, although several candidate biomarkers have been identified so far. As a diagnostic biomarker to recognize overt disease, ELISAs using the human ferritin peptide revealed a positivity of IgG antibodies against ferritin of 92% in GCA and/or PMR patients with a false positive rate of 29% in systemic lupus erythematosus, 3% in RA, 0% in late onset RA and 1% in blood donors [4]. For the detection of response to treatment in active PMR, for example, receiver operating curves analyses of fibrinogen showed higher specificity than either ESR or CRP, with an overall sensitivity and specificity of 92% and 96% [5]. Another group found that plasma IL-6 was more sensitive than ESR for indicating disease activity in untreated and treated GCA patients [8]. These authors pointed out that smouldering disease activity might expose GCA patients to the risk of progressive vascular disease (e.g. formation of aortic aneurysms) and chronic systemic complications such as IL-6-mediated osteopenia. Also persistent elevation of von Willebrand factor during early remission of GCA was considered as a marker for an endothelial activation status induced by a remaining inflammatory microenvironment [7]. Interestingly, optic nerve ischaemia has been associated with increased levels of circulating vascular endothelial growth factor in another Spanish study [8]. As imaging biomarkers, sonography has now been introduced in the 2012 provisional EULAR/ACR classification criteria for PMR, leading to an increased specificity of