

The Role of Environmental Factors in the Pathogenesis of Anti-Neutrophil Antibody Associated Vasculitis

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Abstract

This review seeks to critically examine the environmental factors reported to be associated with anti-neutrophil antibody associated systemic vasculitis. The published literature was searched in a systematic fashion. From this emerges strong evidence for a latitude gradient in the case of granulomatous polyangiitis and eosinophilic granulomatous polyangiitis; both appear more common at high latitudes. Microscopic polyangiitis does not demonstrate this. Latitude affects ultraviolet radiation exposure and the relationship of increased incidence of granulomatous polyangiitis and eosinophilic polyangiitis with decreased ultraviolet radiation exposure is much stronger. The most plausible explanation is vitamin D levels, a hormone known to be vital for normal immune function and largely synthesised in humans secondary to ultraviolet radiation exposure. Case control studies demonstrate a consistent relationship to silica exposure a substance well known to have profound immunological effects. The genetic risk factors for these diseases will be considered and a model of how genes and environment may interact to produce these diseases discussed. Low vitamin D levels, silica exposure, other environmental triggers may interact with genes that influence the immune and inflammatory response to initiate and sustain these diseases. As such, the broad concepts developed about the etiopathogenesis of the anti-neutrophil antibody associated vasculitides shows many parallels to other autoimmune diseases. Much more information is required about both genes and the environment, but the model helps define the questions that need to be answered.

Keywords: Anti-neutrophil antibody; Pathogenesis; Environmental Factors; Vasculitis

Introduction

For decades, generations of students have been taught that autoimmune diseases were caused by environmental factors acting on a background of variable genetic susceptibility. Numerous susceptibility genes with the potential to influence immune function have been identified [1,2], but with the exception of certain drug induced syndromes [3] and gluten sensitive enteropathy [4] evidence about the actual environmental triggers has been lacking and students fobbed off with vague references to infectious agents; viruses and bacteria [3]. Although there is still dearth of evidence about the precise triggers of most autoimmune disease the past few decades have witnessed a considerable expansion in our knowledge of environmental cofactors that appear able to alter the immune system and skew it towards autoimmunity or allergy [5].

This expansion in knowledge has accompanied a significant increase in incidence of many autoimmune diseases over several decades since about the 1970s, clearly too rapidly to reflect any change in the genetic make-up of the various populations studied. The increase has been documented both in organ specific, for example type 1 diabetes [6] and systemic diseases including antineutrophil antibody associated systemic vasculitis (AASV) [7]. The increase in incidence has begged the question of what environmental factors may have changed leading to this. This review will examine this in the context of AASV.

Wegener's granulomatosis (now renamed granulomatous polyangiitis - GPA), microscopic polyangiitis (MPA), the Churg-Strauss syndrome (now renamed eosinophilic granulomatous polyangiitis -EGPA) make up the anti-neutrophil cytoplasmic antibody (ANCA) associated systemic vasculitides - AASV [8]. Clear definitions have really only been available since the development of the classification criteria by the American College of Rheumatology (ACR) in 1990 [9] and the Chapel Hill Consensus Conference (CHCC) in 1994 [10]. The AASV are characterised by necrotising small-vessel vasculitis

with a paucity of immune deposits, seen in renal and other biopsies in association with autoantibodies to cytoplasmic proteins in neutrophils. The predominant specificity of ANCA are proteinase 3 (PR3) and myeloperoxidase (MPO) [11]. Interestingly, although most clinicians would now use ANCA to help arrive at a diagnosis, these criteria do not include ANCA and there is probably need for further refinement of the definitions used for research and clinical purposes [8,12].

Generally, these are diseases of the middle aged and elderly and are particularly rare in children suggesting that environmental factors may predominate over genetic factors. The gender balance of disease incidence is close to unity, quite unlike most systemic autoimmune diseases such as SLE suggesting again the importance of environmental factors. However there are major ethnic differences in the occurrence of different types of AASV and several different examples of major differences between White Caucasians and other ethnic groups living in the same location in the occurrence of all forms of AASV putting genetics firmly back in the frame [13-15].

Methods

The literature has been systematically searched for epidemiological, case control, ecological studies together with specific questions

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about prominent modern risk factors; smoking, obesity, industrial pollutants, sedentary lifestyle and potential infectious causes. PubMed will be the primary search engine (last accessed September 20 2013) with the terms “ANCA associated vasculitis, each of the specific syndromes, “primary systemic vasculitis,” vasculitis” intersecting with “epidemiology”, “ecological study”, “case control study”, “smoking”, “obesity”, “sedentary lifestyle”, “metabolic syndrome”, “vitamin D”, “genetics”. The proceedings of the last three (14th, 15th and 16th) international vasculitis and ANCA workshops and the Asia Pacific meeting of Vasculitis and ANCA workshop, 2012 have been examined for any early relevant reports that may not yet appear in PubMed. The gleaned information has been summarised and the way in which the reported environmental factors may influence the immune system has been discussed in the context of what is known about the pathogenesis of the AASV, including genetic factors to allow a discussion of possible mechanisms.

Results

Epidemiological studies

The published studies, both incidence and prevalence to 2011 have been summarised previously [7,16]. A more recent study from Northern Germany will be included [17]. These reports have largely used a combination of ACR or CHCC definitions as indicated and most have involved multiple strategies to ensure accurate capture of subjects in a particular defined geographic area. Studies that precede the use of these definitions have been excluded. Studies from both the East and West of Asia (Japan and Kuwait) report little or no AASV other than MPA [18,19]. In the case of Japan this appears to be a repeatable conclusion [20]. The nature of case ascertainment in Kuwait may have worked against finding GPA or EGPA without renal disease [19]. Particular attention has been paid to reports of incidence data as prevalence may be affected by improved management and survival [21]. The findings that can be extracted from these studies can be considered under a number of headings.

Age, gender and ethnicity: Overall these studies show that the AASV occur with advancing years with GPA peaking in the middle aged to elderly with a variable but small ratio of males to females (range M:F 1.9-0.5). In this regard, the AASV clearly differ from the female dominated systemic autoimmune diseases – systemic lupus erythematosus, Sjogren’s syndrome and scleroderma and probably differ in important aspects of their pathogenesis [22].

The AASV, in particular GPA are diseases of Caucasians of European origin. This is seen and remarked upon in Europe, the United States of America (USA) and New Zealand (NZ) [13-15]. Specifically in France where there were a substantial number of non-Europeans in the Departments of Greater Paris the overall occurrence of vasculitis was half that seen in the Europeans in the same geographic area [13]. In New York State, African Americans and Hispanics were under-represented in GPA when compared to the population as a whole [14]. In North Carolina African Americans were very under-represented compared to the general population [23]. Similarly, in NZ the rate of GPA amongst Europeans was twice that of the NZ Maoris or Asians [15].

Changes over time: There is evidence suggesting an increase in incidence of AASV over the last several decades. This is particularly evident in data from Scandinavia and Northern Germany. In the three northernmost counties of Norway the annual incidence and prevalence of WG rose from 5.2/million (1984-1988) to 6.5/million (1989-1993) to 12.0/million (1994-1998) [24]. A similar sort of increase was seen

in Sweden [25]. In Germany there appears to be an upward trend with the incidence rates and years as follows: 1998, 11/million; 1999, 9.5/million; 2000, 12/million; 2001, 12/million; 2002, 16/million [26]. A more recent report from the same group and population has confirmed a doubling in AASV from 1994 until 2006 [17]. In Norfolk, UK a lesser rise occurred with AASV as a whole and seems to have plateaued [27]. In South Eastern Australia, the incidence of AASV rose from 13.4/million in 1995-1999 to 15.6/million in 2000-2004 [28]. Some of this increase may have followed the introduction of widespread ANCA testing and a reclassification of idiopathic crescentic glomerulonephritis to MPA, although a number of authorities believe there is more to it than this. Analysis of the trends in more recent years shows that the increase continues, arguing against enhanced diagnosis as a factor [17].

Fluctuations over time: As well as a probable increase over time some studies have peaks and troughs in the disease occurrence, every 4-5 years a peak of WG in Norway [24], similarly every 3-5 years in central Sweden [29] and every 3 years for AASV as a whole in Spain [30]. The group from Norfolk have recently reported a seven year periodicity for WG, but none for MPA [31]. Temporal clustering however has been sought and not found in other studies [32-34]. There are yet no explanations such as infectious disease cycles or UVR fluctuations reported to explain these findings.

The season of onset: The season of onset has been examined in a number of these studies with conflicting results. A winter peak is evident in data from Norfolk and Sweden [29,35]. This pattern is supported by hospital based data from other sources [26,33,34], although in one study it was really a spring/winter peak [36]. A study from the USA reported an increase in autumn and spring [14], from NZ an increase in autumn and decrease in spring [37] and a recent French survey has paradoxically shown a summer peak [38]. This prompted a re-examination of the Norfolk data which now shows a non-significant winter peak, a summer trough and no relation to the serial changes in a number of important upper respiratory tract pathogens [39]. While different factors may contribute to the pathogenesis in different places providing a plausible explanation for these quite different results a number of other studies do not support seasonality at all [24,25]. Indeed, given that patients with AASV will experience a prodromal stage to their illness of quite variable length it is not surprising that such conflicting results are evident and at this stage, no conclusions about etiology can be drawn.

Latitudinal gradient: A latitudinal gradient exists, perhaps shown most elegantly for GPA in Caucasians of European origin NZ where the method of case ascertainment is identical for the whole country [22,37]. A less clear cut gradient is also evident in the northern hemisphere, perhaps because of minor variations in case ascertainment, or ethnic differences [16,40]. The latitudinal differences in the northern hemisphere also relate to the relative frequencies of the different subsets of AASV with GPA predominating in Norway and MPA predominating in Spain and even more so in Japan and Kuwait [18,19]. While ethnic variation may contribute to the latter, the differences between northern and southern Europe are unlikely to be major. Taken with the NZ data make it much more likely that there are environmental factors causing this.

Urban-rural differences: Some studies suggest that GPA is more common in rural areas although most do not have or do not present data to address this issue and no consistent pattern emerges [16,41]. In the Australian Capital Territory and surrounding region there is such a difference, which is interesting as the two major risk factors in our view, UVR, and silica exposure would be in conflict in terms of

the hypothesis presented below and perhaps the balance elsewhere is different.

Ecological study

A subset of these published epidemiological studies where incident data, total population of the study region and age-specific incidence rates and study location was provided has been taken and an ecological study seeking any relationship with measures of ambient Ultra-Violet radiation (UVR) carried out. In contrast to latitude, which changes in a linear manner towards both poles ambient UVR decreases in a geometric fashion as one moves towards the poles, even more so in winter. Ambient UVR was obtained from satellite data using the longitude and latitude of the largest urban centre in any given area. Both the ambient UVR level weighted to erythemally effective wavelengths (UV_{ery}) and to vitamin D effective wavelengths (UV_{vitD}) under both blue sky and cloudy conditions was estimated. Winter UVR as well as mean daily ambient UVR was recorded because there is a stronger latitudinal gradient in winter UVR compared with summer UVR and a known limitation on vitamin D production from available winter UVR at high latitudes. It is noteworthy in our analysis that the data from Kuwait was excluded as the methods of ascertaining cases or the precise denominator population from which the study was drawn was not clear from this publication. The crude incidence rates of both EGPA and GPA increased with latitude, although only GPA achieved statistical significance. Using a negative binomial regression there was a modest increase in the incidence of both EGPA (3.4%) and GPA (3.5%) per a higher degree of latitude. MPA showed no association in either analysis, although it is possible that our exclusion of the data from Kuwait prevented demonstration of a previous negative correlation with latitude [18]. As was predicted the relationships were much stronger with ambient UV radiation with a stronger inverse correlation demonstrable for GPA than EGPA. As expected there was no relationship between any measure of UVR and MPA [21].

Although UVR has local effects on the immune system in the skin [41] and as such is of particular importance in SLE, the most plausible explanation for these findings is through the effects on vitamin D synthesis, a hormone that has profound effects on the immune system which has been reviewed in a wide range of inflammatory rheumatological conditions [42]. There is however no population data on vitamin D from the populations for which we have AASV incident data and no series measuring vitamin D in patients and matched controls.

Case control studies

Nine case control studies have been summarised in previous publications [16,40]. They vary in quality; some had quite small numbers and were probably underpowered. Nevertheless taken together they allow a few conclusions. The dominant risk factor is silica, both crystalline silica and silica found in crop dusts. Silica has a major impact on the immune system, is associated with a number of autoimmune syndromes and is most commonly inhaled, so the results are not so surprising [43]. The association is seen in AASV where there is no respiratory tract disease, suggesting that the impact of silica goes beyond the immediately exposed airways. These findings are supported by other reports of silica associated AASV, including Japanese study from Kobe showing an increased occurrence and severity of AASV for three years after the devastating 1995 earthquake when compared to the unaffected neighbouring Kyoto prefecture. The authors attribute this to dust and other particulate air pollution, the dust contained silica [44].

Silica of course is often not inhaled alone and this needs to be borne in mind. The most interesting conclusion from the Kobe earthquake is that the environmental impact can be quite proximate in a temporal sense that is the effect came and went soon after the original challenge [44]. Heavy metal exposure comes up in some in some studies, as do solvents and pesticides [16,40]. Farming appeared an at risk occupation in a minority of studies; farmers are exposed to silica contained in dust. As has been discussed above when urban and rural differences have been examined the results are conflicting. Allergy and drug allergy (in general) appear in two of the studies [16,40]. Atopy is common, allergy may be over-reported and some of the clinical features, for example, sinusitis may be seen as part of the clinical spectrum of vasculitis itself. Unfortunately, case control reports do not include any data about personal UVR exposure or vitamin D levels.

Infection

Not surprisingly, there has been from the outset a suspicion that infection may trigger episodes of AASV. Infection could be involved in the primary etiology of AASV; infection could trigger episodes of relapse or both [45]. The role of *Staphylococcus aureus* in triggering relapses and the possible mechanisms of action has been explored. Their work demonstrates increase nasal carriage of staphylococci and a correlation between nasal carriage and relapse [46]. Specific types of *Staphylococcus* appear to be present during relapse [47]. However, the role of nasal carriage has been explored in parallel with EUVAS trials with a much less clearcut picture emerging, although the number of swabs taken was far less (D Jayne, unpublished observations). A suggestion that staphylococcal toxic-shock-syndrome-toxin may play a part in GPA [48] is not supported by the nature of the disease where the time frame and pathology are quite unlike that seen in an accepted superantigen induced disease such as the toxic shock syndrome or probable superantigen induced disease such as the vasculitis Kawasaki syndrome [49]. More recently an initially exciting finding provided evidence for molecular mimicry between the human LAMP-2 epitope (a common ANCA specificity) and bacterial adhesion FimH derived from many gram negative organisms [50]. This quite compelling hypothesis remains in limbo as the serological studies have proved difficult to repeat in other laboratories [51].

An observation that a patient who received TMP-SX for a urinary tract infection with *Escherichia coli* had an apparent coincident improvement in their intercurrent GPA lead to TMP-SX being used for induction therapy in GPA, a situation where except perhaps for limited nasal disease its efficacy is suspect and for maintenance therapy, where it appears to have an adjunctive role [52]. While this may represent an antimicrobial effect, there is no proof of that and TMP-SX may also have intrinsic immunosuppressive properties [53].

Cigarette smoking

Cigarette smoke contains multiple active compounds that can potentially interact with the immune system. Any effects could be local in the airways or systemic. All three AASV have prominent respiratory tract features. The data however are less compelling. A small retrospective study showed fewer smokers in patients with AASV than a matched control population [54]. An analysis of patients enrolled in 4 EUVAS sponsored controlled trials and repeated in the Vasculitis Quality of Life study indicated that smokers were more likely to have vasculitis related gastro-intestinal disease than non-smokers [55]. This effect of smoking parallels that observed in Crohn's inflammatory bowel disease but what the observation means in terms of the overall etiopathogenesis of AASV is unclear.

Drugs and toxic chemicals

The above case control series suggest in some cases a general association with drug allergy without being specific. There are more specific associations including propylthiouracil (PTU) which can trigger both ANCA AASV [56]. Some patients have recovered completely on cessation of the PTU, others have required conventional immunosuppressive therapy [56,57]. Hydralazine has been similarly, but less frequently reported [58]. The ANCA seen with drug induced disease appear much more heterogeneous with additional specificities such as lactoferrin, cathepsin G and azurocidin and a long list of less frequent neutrophil antigens [59].

The role of certain classes of medication in precipitating EGPA has been of particular concern. Thus a number of post-marketing surveillance reports have appeared linking EGPA to the use of leukotriene receptor antagonists (LTRA), including both cysteinyl leukotriene receptor blockers – montelukast, zafirlukast and pranlukast and zileuton, a 5 lipoxygenase inhibitor [60]. Some patients may have been prescribed these drugs for severe asthma which was already on the path EGPA, but probably not all [60]. Macrolide antibiotics have been associated with EGPA in a series of case reports [61-63]. In most cases, it is hard to distinguish between the use of a macrolide to treat a putative respiratory tract infection in a patient already developing EGPA and a true association, although in one case there was a positive challenge [63]. Not only is the data in regard to at least some drugs still open to question, but no overall hypothesis pointing to a disease mechanism emerges from these studies. Similarly, although it is popular to blame environmental exposure to all sorts of chemicals or xenobiotics for the occurrence of autoimmunity little emerges from the case control studies and much more work is needed [64].

Obesity and the metabolic syndrome

An increased body mass index, particularly if accompanied by the metabolic syndrome has demonstrable effects on the immune system [65]. Obesity and the metabolic syndrome seem to have a close association with disturbances of the normal gastrointestinal flora [66]. Many health problems are thought to arise from perturbations and in the context of inflammatory syndromes, including potentially many autoimmune diseases obesity and the metabolic syndrome are associated with active innate and acquired immune systems [67]. Studies specific to AASV are so far limited but an increased incidence of metabolic syndrome has been reported in AASV. A follow-up report of outcome is awaited.

Sedentary lifestyle

Regular exercise appears to be anti-inflammatory [68] but there are no studies to date in AASV demonstrating either benefit of exercise or specific detriment of a lack of exercise. Such relationships have been demonstrated in type 1 diabetes [69].

Genetics of AASV

Ethnic differences described above including between White Caucasians in France, the USA and NZ and people of Arab descent, African Americans and Polynesians and Asians respectively suggest that genetics may be important [13-15]. Genetic studies in AASV include a number of case control studies exploring plausible risk genes and a recent genome wide association study (GWAS) [70]. All three syndromes are rare in children, occurring in the middle aged to elderly suggesting that genetic effects are not particularly strong. Familial clustering, unlike many other autoimmune syndromes appears to

be quite rare [71]. Most susceptibility genes in autoimmune diseases encode a phenotype that interacts with the immune system; some susceptibility genes affect the putative autoantigens. In considering susceptibility genes consideration will be given as to their possible mode of action, after all such pathophysiological studies will give us the complete picture hinted at by genetic findings.

Known genetic associations include genes that encode proteins known to be important in T cell activation. All of these genetic associations are quite weak with odds ratios of 2-3 generally. There are some MHC class II linkages; DP1*0401 with GPA and MPA in Caucasians and DRB1*0901 with MPA in Japanese and DRB4 with EGPA [72-75]. An allelic form of CTLA-4, a negative regulator of T cell activation encodes a less efficient protein which would be associated with persistent immune activity [73]. In contrast the gene (T1858) encoding the lymphoid tyrosine phosphatase (PTPN-22) encodes an allelic variant Lyp*W620, increased in GPA and MPA, which is a less effective regulator of T cell activity, unless one speculates that this factor is more active in regulatory T cells its actions seem at odds with expectations. There remains some contention about the mechanism of this protein in human cells [76]. There is also an association of variants of CD226 that would increase integrin-mediated activation of naive cells [73].

There is also an association with genes and their products involved in inflammation. GPA is associated with the dysfunctional alpha-1 antitrypsin alleles, Z and S [77]. The association with increased copy number of FCRG3B is however disputed in GPA, but reported in EGPA [72,78].

The GWAS confirmed the association in white Europeans of HLA DBP1*0401, the SERPINA1 locus which encodes alpha-1-antitrypsin and added the PRTN 3 locus which encodes PR3. The relationships are strongest with PR3-ANCA positive subjects. A weaker association between MPO positive subjects and HLA-DQ was noted. The study was not powered to examine details. It is noteworthy in the study that all associations were stronger with the antibody profile, anti-PR3 and MPO [70].

Discussion

The discussion will be focussed on drawing these factors into current plausible models for these 3 diseases bearing in mind that despite their similarities there almost certainly are distinct etiopathogenetic pathways in the different syndromes [79]. The principal aim of the discussion is to ensure that any models of disease pathogenesis takes account of the relevant environmental and genetic factors discovered to date and described here. The one fact that is certain in regard to putative etiologic factors is that our current knowledge is incomplete and as such concepts about etiopathogenesis must be somewhat speculative. To ground these consideration will be given to the better publicised current models [11,79,80]. These models do tend to be overarching and endeavour to account for all forms of AASV, or at least GPA and MPA whereas both the genetic and environmental differences suggest that there may be common and different pathways. Class 2 MHC genes are associated with all three forms of AASV although the risk alleles are distinctly different for each and not yet identified in every ethnic group studied. Overall this is consistent with the idea that antigen under MHC control is being presented to CD4 T cells. The different MHC relationships suggest that the antigens may be different. This is in accord with current understanding, PR3 and MPO being important antigens in GPA and MPA respectively. EGPA provides a problem in that a significant number of cases are MPO-ANCA negative. Those with

glomerulonephritis that show more clinical overlap with other AASV tend to be MPO-ANCA positive [81]. Based upon the environmental and genetic findings described so far, animal models and ex vivo studies in AASV a model that accounts for the current known facts has been proposed by a number of groups [11,79,80]. A number of assumptions appear to have been made in these reviews, which can be challenged. Firstly, although the evidence from both animal models and passive transplacental acquisition of transient MPA that anti-MPO ANCA play a role in the pathogenesis of MPA is quite strong neither convincing animal models nor a human experiment of nature have been documented for anti-PR3 [11]. A role of the diagnostic or marker antibodies in actual disease pathogenesis cannot be assumed and given that renal biopsies are largely pauci-immune the role of CD4 T cells, particularly in PR3 associated disease may be as effectors, not just as potential controllers of auto-antibody synthesis. The recurrence of both GPA and MPA after B cell and ANCA depletion with rituximab without the return of ANCA also argues against an indispensable role of ANCA [82]. The findings about PR3 in the GWAS provide further support for the importance of this protein as an autoantigen [70]. The additional genetic factors so far identified would most likely play a role in modifying the autoimmune response as it develops. Encoded allelic differences in those discovered so far, CTLA-4 and PTPN-22 would operate at a T cell level. The allele encoded in the case of CTLA-4 in fact does act to make negative regulation less efficient and could be expected to be associated with exuberant immune reactivity [73]. The PTPN-22 allelic variant increased in both GPA and MPA would at first sight appear to operate in the converse direction and creates a problem with the hypothesis unless it is more active in regulatory T cells. This gene is however very interesting when seeking explanations for the major ethnic differences. This allele is quite common in White Caucasians and quite rare in other ethnic groups. Does that contribute to the restricted occurrence of GPA in this ethnic group? Further work will be needed to answer this question. Once a T cell driven response occurs neutrophils feature prominently in GPA and MPA and genes that would enhance neutrophil activity such as those encoding dysfunctional alpha-1-antitrypsin would be expected to play a role here. The genetic influences are each on their own relatively weak, but appear to act to up-regulate lymphocyte activity and the concept of quantitative thresholds for immune-cell signalling has allowed an understanding of how multiple genetic factors of a relatively small effect may combine to create a state of susceptibility to autoimmunity [2].

The environmental observations show both overlap between syndromes but also clear and profound differences and the current proposed models include a degree of homogeneity in regard to the pathogenesis of the three syndromes that is not justified by the literature quoted in support and indeed quite different, albeit overlapping mechanisms may be expected [11,80]. At this time the dilemma is most readily resolved by separating out the pathogenesis of granulomas, seen in GPA and EGPA from necrotising vasculitis involving small arteries, arterioles, capillaries and venules, common to all three syndromes [11,79,80]. Current evidence suggests that the vasculitic lesions involve neutrophil activation, possibly abetted by ANCA and consequent neutrophil enzyme and other product mediated vascular damage [11,80]. As TH17 cells predominate in the capacity to recruit neutrophils, these T cells are probably involved and if antibody production is really integral to the development of vasculitis then TH2 cells are presumably involved [11]. Granulomas are generally regarded as a product of disturbed innate and cellular immunity and in the context of GPA and potentially EGPA with overactive Th1 and TH17 cells and a reduction in numbers and/or activity of Treg cells [83,84].

The known environmental factors can be reconciled with this model. The impact of low vitamin D, in turn secondary to low UVR would be manifest through increased TH1 and Th17 and decreased Tregs and associated with granuloma formation, consistent with the latitudinal gradient seen with both GPA and EGPA, but not MPA where there are no granulomas [85]. Silica exposure has been associated with decreased Tregs and increased Th17 [43] and has been shown to bind to the neutrophil peptide LL-37 and induce ANCA antigen synthesis and could undoubtedly play a role in all three syndromes [86]. The role of infection remains unclear for while there is broad agreement that infectious agents may trigger attacks, the concept that specific agents such as *S. aureus* or gram negative organisms generally are involved remains under question [45-48].

EGPA warrants a further comment. The favourable effect of therapy that decreases eosinophils suggests that this cell plays a pivotal role in the pathogenesis of EGPA. T cells appear to be vital and through IL-5 eosinophils are under T cell control. This together with IgE production indicate that there is a TH2 response. Th1 and TH17 have been reported and could drive the granulomatous component of the diseases [87].

In conclusion, the nature of both genetic and environmental risk factors in the AASV is becoming clearer although by no means complete. Many can be entered into a plausible understanding of the disease pathogenesis, or at this stage in our understanding provide hypotheses that can be tested.

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