A little help from our friends: what an epidemiologic study teaches us about autoinflammation, granuloma and proteinase-3-specific antineutrophil cytoplasmic autoantibodies

Peter Lamprecht and Wolfgang L. Gross

University of Lübeck, Department of Rheumatology, Vasculitis Center UKSH & Rheumaklinik Bad Bramstedt, Ratzeburger Allee 160, 23538 Lübeck, Germany

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The standard epidemiologic approach to complex diseases tracks down differences in incidence and prevalence rates between distinct populations. Thereby, the potential impact of genetic susceptibility and/or environmental factors will be elucidated and can be dissected on the molecular biologic level in further studies. In this journal issue of Nephrology Dialysis Transplantation, Watts et al. [1] report on the incidence of renal vasculitis in a population from the Norwich area, UK. The authors compared these data on renal involvement in the three anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides (AAV) Wegener’s granulomatosis (WG), microscopic polyangiitis (MPA) and Churg Strauss syndrome (CSS), to recently published incidence rates of a Japanese population [1,2]. The overall incidence rate of renal vasculitis was similar in the UK and Japan (12.2/10^6 versus 14.8/10^6). The incidence of WG (5.8/10^6) in the UK was slightly lower, that of MPA (4.9/10^6) slightly higher and that of CSS (1.4/10^6) comparable to that of newly diagnosed WG, MPA and CSS patients in central Europe [1,3]. However, no WG or CSS patients were seen between 2000 and 2004 in the Japanese study. All patients with renal vasculitis were diagnosed to suffer from MPA (incidence 14.8/10^6). ANCA with a cytoplasmic fluorescence pattern (C-ANCA) and proteinase-3-specific (PR3)-ANCA were not detected among renal vasculitis patients in Japan. ENT involvement was virtually absent and neurological involvement was significantly less frequently diagnosed in renal vasculitis patients from Japan as compared to those from the UK [1,2].

Caveats with respect to this study regard the comparison of data from a prospective (UK) and a retrospective (Japan) study (as pointed out by the authors), comparing data from a hospital-based survey (single referral centre in Norwich, UK) with a population-based analysis of the incidence of AAV (Miyazaki Prefecture, Japan), and the lack of information, how ENT, respiratory, neurological and gastrointestinal involvement were determined. For instance, the history or a questionnaire on ENT-involvement could be biased by memory, attention and other reasons. Inspection with or without further endoscopic viewing by an ENT specialist plus a MRT scan of the head demonstrating signal intensity suggestive of inflammatory tissue in the sinuses and further signs of vasculitis discloses previously unsuspected and unrecognized involvement of

Correspondence and offprint requests to: Peter Lamprecht, MD, University of Luebeck, Vasculitis Center UKSH & Rheumaklinik Bad Bramstedt, Ratzeburger Allee 160, 23538 Luebeck, Germany. Tel: +0049-451-500-2368; Fax: +0049-451-500-3650; E-mail: peter.lamprecht@rheuma.uni-luebeck.de

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the upper respiratory tract. ENT involvement (and potentially that of other organs as well) is understated in many studies because of a lack of diagnostic effort [4]. Moreover, patients with localized WG, early systemic WG or MPA, or AAV with mild renal involvement might attend rheumatologists, ENT-specialists or pulmonologists rather than nephrologists in the first place (Table 1) [5,6]. Ideally, patients should be diagnosed in the early stage of AAV before disease progression to severe renal dysfunction occurs. Further, renal involvement is seen in only about one quarter of CSS patients [7]. Thus, renal vasculitis is not a synonym for systemic vasculitis in AAV. The incidence rates reported in this study [1] refer to patients with AAV and renal involvement rather than AAV patients displaying early stages or oligosymptomatic variants of the diseases—even though most AAV patients might have been seen by the referral centre in this study.

Another point of concern is the presence of ANCA to diagnose AAV [1]. Although circulating PR3-ANCA are the serological hallmark of WG, PR3-ANCA are detected infrequently during the initial phases of WG (localized and early systemic WG). In contrast, PR3-ANCA are nearly always detected in generalized WG (95% of patients) [8]. Whereas PR3-ANCA are highly specific for WG, myeloperoxidase-specific (MPO)-ANCA are detected in only ~60–70% of MPA patients. MPO-ANCA and PR3-ANCA are also present in CSS, albeit even less frequently (10–50%) [9]. Thus, there is a substantial part of MPA and CSS patients, who remain ANCA-negative. The spectrum of disease differs between ANCA-positive and -negative MPA and CSS patients. Renal involvement is much higher and the clinical spectrum different in ANCA-positive MPA and CSS patients as compared to ANCA-negative patients [7,10]. A recent study showed an increased frequency of the HLA-DRBI*07 allele in CSS that was not found for WG in previous studies [11]. ANCA-negative CSS, but not ANCA-positive CSS or WG, is associated with the interleukin (IL)-10.2 haplotype [12]. These genetic and clinical aspects challenge the view that WG, MPA and CSS represent phenotypic variants of the same entity, AAV, rather than being three unique diseases sharing ANCA positivity as a potential outcome and to different extents [13,14].

In this context, comparison of the disease manifestations and ANCA-specificity in AAV between the UK and Japan is one of the great merits of this study [1]. ENT involvement and PR3-ANCA are typical clinical and serological features, respectively, of WG [15]. PR3-ANCA was not detected, ENT-involvement hardly ever seen and WG not diagnosed in the Japanese population in 5 years. Instead, MPA, which usually displays no ENT involvement and often is MPO-ANCA positive, was the only AAV seen in Japan [1]. Intriguingly, this observation reflects WG pathogenesis. The WG autoantigen, PR3, is a neutrophil- and monocyte-derived serine protease with an astonishingly broad spectrum of functions including elastino- and proteolysis, antimicrobial action and maturation of myeloid cells (‘myeloblastin’). PR3 cleaves and enhances the activity of the proinflammatory cytokine IL-32 and procaspase-3 resulting in macrophage activation and prolonging neutrophil survival, respectively [16,17]. PR3 induces DC maturation via the protease-activated receptor (PAR)-2 and evokes an exaggerated Th1-type response in WG [18]. Both PR3 and PR3-ANCA enhance local inflammation in animal models [19,20]. Thus, PR3 displays features of an endogenous ‘danger signal’ inducing autoinflammation reminiscent of monosodium urate- or nucleic acid-mediated activation of innate immunity in gout and systemic lupus erythematosus, respectively. Genetic risk factors favouring inflammation (e.g. low FcyReceptor-IIlb (FCGR3B) copy numbers and HLA-DPB1*0401-, RING1- and RXRB polymorphism) and further endogenous and/or exogenous determinants (e.g. S. aureus colonization of the upper respiratory epithelial interface in WG) could link autoinflammation, granuloma formation preferentially affecting the upper respiratory tract and autoimmunity with PR3-ANCA formation and AAV in WG [21–25]. Of note, WG granulomata display lymphoid-like structures, which could sustain autoimmunity to PR3 [26,27]. Therefore, the absence of ENT involvement, i.e. upper respiratory tract involvement, linked to the absence of PR3-ANCA—as observed in the study by Watts et al. and Fujimoto et al. [1,2]—supports a pathophysiological concept in which granulomatous inflammation of the respiratory barrier is linked to autoimmunity in WG [26,27].

Conflicts of interest statement. None declared.

(See related article by R. A. Watts et al. Renal vasculitis in Japan and the UK—are there differences in epidemiology and clinical phenotype? Nephrol Dial Transplant 2008; 23: 3928–3931.)
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