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Review

Granulomatosis with polyangiitis and facial palsy: Literature review and insight in the autoimmune pathogenesis☆

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ABSTRACT

Granulomatosis with polyangiitis (GPA) is an autoimmune systemic necrotizing small-vessel vasculitis associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCA). Oto-neurological manifestations of ANCA-associated vasculitis according to PR3-ANCA positivity and MPO-ANCA positivity are usually reported.
Facial nerve palsy is usually reported during the clinical course of the disease but it might appear as the presenting sign of GPA. Necrotizing vasculitis of the facial nerve 'vasa nervorum' is nowadays the most widely accepted etiopathogenetic theory to explain facial damage in GPA patients. A central role for PR3-ANCA in the pathophysiology of vasculitis in GPA patients with oto-neurological manifestation is reported.
GPA requires prompt, effective management of the acute and chronic manifestations. Once the diagnosis of GPA has been established, clinicians should devise an appropriate treatment strategy for each individual patient, based on current clinical evidence, treatment guidelines and recommendations.

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Abbreviations: GPA, granulomatosis with polyangiitis; ANCA, anti-neutrophil cytoplasmic antibodies; PR3, proteinase 3; MPO, myeloperoxidase; LAMP-2, lysosome-associated membrane protein-2; TNF-α, tumor necrosis factor alpha; NCGN, necrotizing crescentic glomerulonephritis; EUVAS, European Vasculitis Study Group; IAH, intra-alveolar hemorrhage; ENT, ear nose throat; AICA, anterior inferior cerebellar artery; HBS, House–Brackmann scale; OM, otitis media; CT, computed tomography; MRI, magnetic resonance imaging; IFN-γ, interferon γ; ELISA, enzyme-linked immunosorbent assay; ESR, erythrocyte sedimentation rate.

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1. Introduction

Granulomatosis with polyangiitis (GPA) is an autoimmune systemic necrotizing small-vessel vasculitis associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCA) with a cytoplasmic staining pattern usually directed against proteinase 3 (PR3) [1–3].

It was first described in the medical literature in a clinical case report in the late 19th century and was formerly known by the eponymous name, Wegener's granulomatosis, after Friedrich Wegener who described the clinical triad of lungs, kidney and upper respiratory airways involvement associated with this disease in 1936 [1,4,5].

Since 2011, Wegener's granulomatosis has been known as granulomatosis with polyangiitis (GPA) [1–3].

The annual incidence of GPA is 10 cases per million population, with an equal frequency in males and females and is very rare in childhood and young adults. The reported peak incidence of GPA is in the 7th decade of life, between the ages of 65 and 70 years [6].

In this review, the authors focus on the otologic manifestation of GPA, particularly on VII cranial nerve paralysis, a rare clinical manifestation of GPA. The pathogenesis of vasculitis with facial damage and its proper management are also discussed.

The objectives of this review are: (1) to describe the main otologic manifestation, particularly VII cranial nerve paralysis associated with GPA; (2) to define in the pathogenesis of vasculitis with facial damage; (3) to summarize current therapeutic options for GPA patients suffering from facial palsy.

A search in the MEDLINE database for English language articles published between January 1990 and December 2015 was performed. Terms included were ANCA-associated vasculitis, small vessel vasculitis, granulomatosis with polyangiitis and Wegener's granulomatosis, in combination with keywords indicative of an ontological involvement such as ENT, middle ear, facial nerve palsy, hearing loss, otitis media and mastoiditis. The full text of relevant articles was retrieved and reviewed by all authors.

2. Etiopathogenesis of GPA

The autoimmune etiopathogenesis of GPA is complex and involves the generation of anti-neutrophil cytoplasmic antibodies (ANCA) against proteinase 3 (PR3) in approximately 80% of GPA patients and against myeloperoxidase (MPO) in approximately 10% of GPA patients [1,6,7]. Antibodies against lysosome-associated membrane protein-2 (LAMP-2) may also play a role in the pathogenesis of GPA via a process of molecular mimicry. In GPA, PR3 is the principal target antigen of ANCA. Several in vitro and animal models using different approaches support the concept that an interaction of PR3-ANCA with PR3 released from azurophylic granula and expressed on the cell surface of TNF-α-primed neutrophil granulocytes results in premature degranulation of neutrophil granulocytes, subsequent endothelial cell damage, and leukocyte recruitment [1,7–9].

Falk et al. [10] demonstrated that the antibodies, and even their F(ab′)2 fragments, although to a lesser extent, could induce the production of reactive oxygen species and the release of lytic enzymes such as õelastase and PR3 by donor neutrophils. In order to become activated by ANCA, neutrophils must be in a state of pre-activation (primed). Priming occurs in the presence of low amounts of pro-inflammatory cytokines such as tumor necrosis factor-α (TNFα) or interleukin-1. During priming, the target antigens of ANCA, namely, PR3 and MPO, are expressed on the cell surface and thus become accessible for interaction with ANCA. This interaction, which is followed by activation of neutrophils, only occurs when neutrophils are adherent to a surface, a process in which β2-integrins are involved [11]. In vivo, this process is assumed to occur at the endothelial surface. Indeed, activated neutrophils, adherent to the endothelium, are observed in renal biopsies from patients with ANCA-associated NCGN [12]. ANCA-induced neutrophil activation involves not only binding of the antibodies via their F(ab′)2 fragments to surface expressed PR3 or MPO but also the interaction of their Fc-fragments with Fc-receptors on neutrophils, particularly with the FcγRIIa-receptor [13], although F(ab′)2 fragments also have some activating potential [14].

Moreover, other in vitro effects, in particular of PR3-ANCA, have been identified [1–3]. PR3-ANCA can interfere with the proteolytic activity of PR3 [15]. These interfering antibodies may hence act as alternative inhibitors. However, at the site of inflammation, PR3 can cleave these inhibiting ANCA, leaving active PR3 [16,17]. PR3 can also interfere with the binding of PR3 to its physiological inhibitor α1-antitrypsin.

Changes in various in vitro effects of (PR3-) ANCA have been suggested to follow changes in disease activity more accurately than changes in ANCA titers alone, but this suggestion is based on observations of small numbers of patients only and so far remains to be proven [15–17].

Finally, it should be remembered that microbial agent infections, in particular *Staphylococcus aureus*, environmental, chemical, toxic or pharmacological triggers in people who are genetically predisposed to this autoimmune disease have been suggested to be associated with ANCA-associated vasculitis [1,2].

3. Disease stages

The European Vasculitis Study Group (EUVAS) [18,19] classified the disease stages of Wegener granulomatosis based on clinical and pathologic considerations as (1)"*localized*" Wegener's granulomatosis, defined as Wegener's granulomatosis restricted to the upper and/or lower respiratory tract; (2) "*early systemic*" Wegener's granulomatosis involves any organ except renal or imminent vital organ failure; (3) "*generalized*" Wegener's granulomatosis includes renal involvement and/or imminent organ failure.

The disease usually progresses from localized to early systemic and generalized Wegener's granulomatosis within a variable period of time ranging from weeks to years in most patients. However, in a small fraction of patients (≤5%) the disease remains "localized" or "early systemic" for a long time for as yet unknown reasons [1–4,18,19].

4. Clinical manifestations of GPA

According to disease stage classification from EUVAS and expert opinions, at least two different phenotypes can be distinguished in GPA, with the two forms described as localized/limited and systemic/generalized [2]. The different GPA phenotypes are summarized in Table 1.

The clinical spectrum of diffuse forms includes the life-threatening pulmonary-renal syndrome, renal involvement (rapidly progressive glomerular nephritis with necrotizing glomerular tufts) lung involvement with intra-alveolar hemorrhage (IAH) or interstitial pneumonia; cardiovascular involvement clinically manifests with small vessel vasculitis, occlusive vascular disease, pericarditis, pericardial effusions,