
Nasal barrier dysfunction in Wegener's granulomatosis

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Wegener's granulomatosis (WG) is known to be a systemic autoimmune disease. Treatment of disease manifestations on lung and kidney was the fundamental challenge over the past decades. Since the first description as a discrete disease entity in the 1930s, diagnosis of WG often is difficult (1, 2). Initiation of anti-neutrophil cytoplasm antibodies (ANCA) directed against proteinase 3 in the diagnostics in the 1980s was a big step forward, but often with false negative results, especially in cases of localised WG (3). Little attention is given to the upper respiratory tract, even though WG is known to start here and recent studies showed a subgroup of patients remaining in localised WG rather than developing generalised disease.

Via the introduction of modern immunosuppressive treatment by Fauci (4) in the 1980s and protocol adjustment in well defined situations by several groups till today, the clinical course of WG has changed from organ and/or life threatening disease towards chronic recurrent disease with relative mortality risk equal to healthy people. Today, grumbling disease with the sole involvement of nasal and paranasal tissue in patients under immunosuppressive therapy is frequent. However, precise and critical endoscopic examination of the upper respiratory tract by an experienced otorhinolaryngologist (ORL) is demanding to detect clinical hints for WG early. Considering this rare disease, the ORL will often be the first to diagnose WG correctly. Examinations such as MR- or CT scan could support the clinical examination in special situations *e.g.* sinusitis with orbital or cerebral complications but are not superior to easy and cost-efficient clinical examinations in daily routine. Without doubt, further diagnostics and therapy is a collaboration task for the rheumatologist, radiologist, ophthalmologist, dermatologist, pathologist and others.

The ORL is not only required in primary diagnostics but also in routine examinations on patients under therapy for detecting signs of local activity (mainly on nasal tissue) that should lead to therapy adjustment even though there are no other signs of activity as mentioned above.

In popular activity and damage scores such as BVAS or VDI possible signs of involvement of the upper respiratory tract are integrated but very unspecific. For example, "golden crusts" are very unspecific and are not verified to be signs of activity in WG. On the other hand, assessment of the endonasal endoscopic picture is challenging and the inter- and intra-rater variability is unknown and subject to current research. Taken together, the ORL is essential in primary diagnostics of Wegener's granulomatosis and should be integrated in routine examinations for therapy monitoring as well as therapy adjustment. In the future, signs of endonasal activity have to be defined and inter-observer reliability has to be achieved.

The reason for primary and often sole involvement of the nasal and paranasal mucosa is unknown. Remarkably recent studies support the hypothesis of a barrier dysfunction with genetic susceptibility and altered bacterial colonisation in the upper respiratory tract that is comparable to barrier diseases such as Crohn's disease and psoriasis.

In this issue of *Clinical and Experimental Rheumatology* we publish our data for nasal *Staphylococcus aureus* colonisation rates in WG patients compared to healthy and disease controls which support the hypothesis of an imbalance of the nasal microbiome in WG (5). In addition, our group found interleukin 8 which is involved in tissue remodeling (neovascularisation and activation of metalloproteinases) and activation of defence mechanisms (granulocytes and T-cells) to be reduced in challenge

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of nasal epithelial cell cultures (NEC) of WG patients with *S. aureus*. Furthermore, we observed a reduced ciliary beat frequency of the nasal mucosa in WG which might cause prolonged contact of potentially harmful airborne factors (microorganisms as well as inorganic substances) leading to intensified burden of the nasal barrier. In addition, NEC of WG-patients show a reduced hBD-3 response to *S. aureus* challenge, possibly being a reason for the higher nasal carriage rates of *S. aureus* in WG patients. Taken together, results obtained on RNA-, protein- and functional level support the hypothesis of a disturbed mucosal barrier of the upper respiratory tract in WG-patients. Knowledge about these dysfunctions might lead to novel therapies. Decreased levels of antimicrobial peptides (AMP) in WG patients

might be compensated by locally applied AMP, and ciliar dysfunction should lead to avoidance of factors impairing ciliar function such as locally active drugs like steroids, decongestants and smoking. Even though knowledge about certain aspects of WG grows rapidly further studies have to be performed to gain a better understanding of the complex local nasal defence system and to detect the link between this barrier dysfunction and systemic autoimmune vasculitis. In the future, scientists and clinicians will have to undertake every possible effort to optimise diagnostics and therapy for patients suffering from this challenging and multi-faceted disease, possibly starting as a barrier dysfunction in the upper respiratory tract and evolving to generalised autoimmune disease by, until now, an unknown trigger.

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