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Short Communication

Sarcoidosis and Alpha-1-Antitrypsin Deficiency: A Perfect (And Undesirable) Storm

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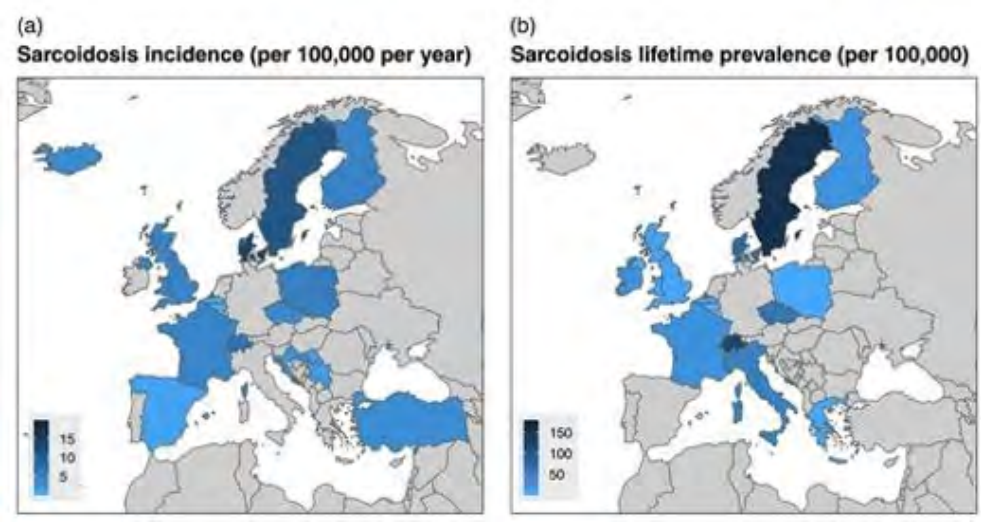
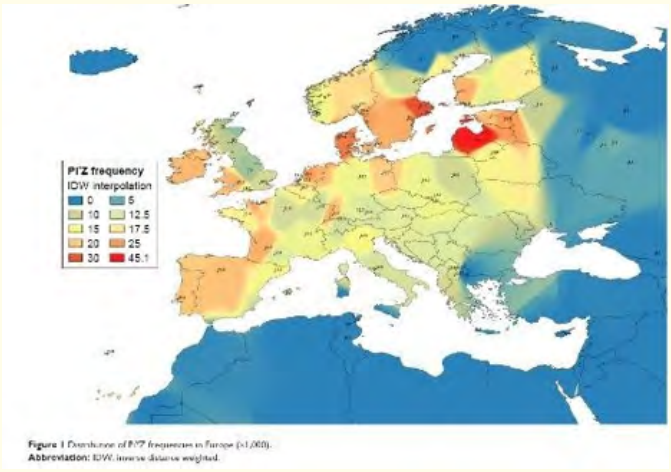
Sarcoidosis and alpha-1-antitrypsin deficiency are two rare systemic diseases frequently leading to chronic pulmonary involvement. Pulmonary involvement is present in 90% of cases of sarcoidosis; the prevalence of this chronic, granulomatous disease is very variable according to geography and race, but an increase in prevalence of around 9% was registered from 1990 to 2020s. Disease burden was particularly important in countries like Italy [1]. Prevalence of alpha-1-antitrypsin deficiency (AATD) is variable too, with a percent in COPD patients until 1.5%, but nowadays this condition is often underdiagnosed. Firstly described in 60s in Swedish population, AATD is a rare genetic disorder caused by mutations in the SERPINA1 gene, which encodes a critical protein involved in protecting lung tissue from damage caused by neutrophil elastase [2].



Source: *Rossides M, Darlington P, Kullberg S, Arkema EV. Sarcoidosis: Epidemiology and clinical insights. J Intern Med. 2023; 293: 668-680.*



Source: *Blanco I, Bueno P, Diego I, Pérez-Holanda S, Casas-Maldonado F, Esquinas C, Miravitlles M. Alpha-1 antitrypsin Pi*Z gene frequency and Pi*ZZ genotype numbers worldwide: an update. Int J Chron Obstruct Pulmon Dis. 2017;12:561-569. https://doi.org/10.2147/COPD.S125389*

GRADS study (standing for Genomic Research in Alpha-1-antitrypsin Deficiency and Sarcoidosis) was an observational cohort study designed to detect interactions between genome and modifiable traits in these two orphan diseases, including microbiome.

The former sarcoidosis protocol was developed analysing 400 participants with a diagnosis established by ATS/ERS criteria without severe or autoimmune comorbid conditions, severe functional impairment, active smoke, ongoing infections. They were studied with self-administered questionnaires, physical and functional exams, a chest CT scan, and eventually research BAL. The associations studied were between specific autoantibodies and different organ involvements (e.g. ANA positivity associated with lung involvement), the amount of IgM/IgG, certains chemokines and disease severity, but also radiation exposure and cardiac affection. Importance of obesity as a significative independent risk factor for sarcoidosis has been stressed, since it promotes a deep proinflammatory lung milieu; in fact obesity and sarcoidosis share high levels of IL- 15, that is also potentially involved in prednisone response [3]. On microbiome side, epidemiological and microbiological studies suggest that, at least in a fraction of patients, microbes or their products may trigger the immune response leading to sarcoid granuloma formation in presence of genetic predisposition. Although in this kind of patients there isn't a microbe signature yet, *mTB* and *C. acnes* seem to be the most frequent candidates [4].

The AATD GRADS protocol was a prospective, multicenter, cross-sectional study of adults older than age 35 with PiZZ or PiMZ alpha-1 antitrypsin genotypes; as in the sarcoidosis protocol, they shouldn't present severe comorbidities or severe functional impairment, and they shouldn't have autoimmune coexisting conditions. The study tried to investigate the interactions between AATD, COPD phenotypes and microbiome. Lung microbiota composition in COPD has been shown to be influenced by age and inhaled corticosteroids, but chronic processes in AATD are more poorly defined. Invasive pulmonary nontuberculous mycobacterial infections were shown to be more prevalent in presence of AATD, and a certain permissiveness was seen for growth of HIV Type 1 [5].

We still don't know enough about the complexity of lung microbiota in chronic diseases; it would be interesting to understand if these diseases can share the same microbial milieu, if their association in a single patient can lead to an augmented superinfection risk, or if the inflammatory dysregulation itself, in AATD lungs, can act as a trigger for sarcoidosis expression. We can assert that in both there is an immune shift versus Th1 response, and this assumption is even stronger considering smokers lungs (where neutrophilic response acts

more). Potentially, patients with AATD could meet a big progression and exacerbation booster in presence of autoimmune granulomatosis reactions, undergoing a deeper reshaping of lungs architecture and thus faster decreasing in lung function, as well as patients with sarcoidosis could develop deeper tissue damages and larger recovery times in presence of AATD. If these suppositions were proven, many (spontaneous) questions would need to be answered: in sarcoidosis patients with AATD should we start earlier anti-inflammatory treatment despite of organ involvement? In AATD patients with sarcoidosis should we choose an earlier augmentation therapy despite of blood amount and/or clinical and functional worsening?

A study about serum levels of AAT in presence of various lung comorbidities was conducted and published in 2025 by Paska., *et al*. [6]. They demonstrated that patients with sarcoidosis and AATD had the lowest serum levels of AAT in comparison with other respiratory diseases like COPD (considering active or previous smokers), cystic fibrosis, asthma and interstitial lung diseases. Patients with ILD and sarcoidosis, instead, were shown to have similar levels in comparison with ILD AATD patients. This conclusion is in contrast with the previous, 70's idea that in active sarcoidosis AAT is higher in blood [7] but opens new scenarios about different sarcoidosis patterns; is there a different AAT activation in patients with a fibrotic evolution of a granulomatous disease, and can AAT act like an independent risk factor for organ architecture subversion? Are there specific AATD genotypes more implicated in this association?

Conclusion

In our precision medicine era studying this complex relation, eventually detecting early biological biomarkers, could be very useful to predict, and thus to prevent, the natural course of these two diseases, ideally leading to a stricter and personalised follow-up in selected patients.

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