Uncovering the Risk of Inhalational Exposures Across Interstitial Lung Diseases

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Environmental and workplace inhalational exposure to organic and inorganic particles can produce a wide range of adverse lung consequences and are modifiable contributors to the burden of chronic respiratory diseases globally. There are several compelling reasons to pursue the search for an environmental and occupational exposure cause in all patients with chronic respiratory diseases, particularly those with newly detected interstitial lung disease (ILD).

Knowledge of the inciting antigen exposure can help establish pretest estimates of disease likelihood, may affect patient treatment and prognosis, and is critical to the prevention of further disease progression. The reduction of such exposures could even lead to the amelioration of the ILD in its early stages. For instance, a long-term decline in pneumoconiosis-associated deaths in the United States has been attributed partly to secondary prevention through early disease detection and implementation of exposure prevention initiatives in the workplace.1

Although genetic susceptibility can alter the initiation and trajectory of ILDs, environmental triggers are crucial determinants. At one end of the spectrum, inhaled organic or inorganic particle contribution to hypersensitivity pneumonitis (HP) or pneumoconiosis development and worsening might be easy to recognize. Although far less obvious, such exposures can also be identified in patients with noninhalational ILD. For example, data from a Canadian registry of pulmonary fibrosis showed that exposure to hot tubs and down feathers were reported similarly in patients with ILD with and without HP.2 Moreover, a large population-based study in Denmark showed a 33% increased risk for non-HP ILD among pigeon breeders compared with the referent population.7 A significant challenge is to demonstrate that the exposure is clinically relevant and causally related to the ILD. We may consider what might a particular environment do to a patient with noninhalational ILD to see whether there is evidence of clinically appreciable changes in symptomatic, physiologic, and radiographic features. In this group of patients, the effect of inhalational exposures started to be appreciated in recent decades, mainly because of mounting evidence that suggests an association between occupational exposures and idiopathic pulmonary fibrosis (IPF). Several case-control studies have strengthened this relationship; some of them have shown a dose-response.3,6 Although these studies have focused primarily on IPF, the type, prevalence, and possibly harmful effects from inhalational exposures remain understudied across a wide variety of ILD diagnoses.

In this issue of CHEST, Lee et al7 tested the hypothesis that, in patients with ILD, regardless of specific multidisciplinary diagnosis, inhalational exposures would be common, have differential prevalence by sex and race, and be associated with worse pulmonary function and survival compared with patients with ILD without exposures.

Within a single-center cohort of 156 patients with ILD, 101 patients (65%) had a history of potentially relevant inhalational exposure. As suggested by the literature, the investigators found that, although patients with HP were overall more likely to have a history of an inhalational exposure (91%), 83% of patients with IPF, 45% of patients with connective tissue disease-associated ILD, and 64% of patients with interstitial pneumonia with autoimmune features also had a relevant exposure history.2,4 Domestic exposures (ie, mold, bird, or hobbies associated with ILD) were more frequent than multiple (≥1 at work and/or home) or occupational

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exposures (e.g., organic, silica, metal): 74 patients (47%) vs 62 patients (40%) vs 59 patients (38%), respectively.

The authors found that more men than women had any inhalational history. Like prior reports, a higher proportion of men had a history of occupational exposures (66% vs 14% of women). Although sex differences have been implicated in the prevalence and presentation of connective tissue disease-associated ILD, HP and IPF, this study did not control potential confounding associations between workplace characteristics and sex across patients with ILD.

When exposures were stratified by race, no differences were seen in the prevalence of occupational or mold exposures. However, the odds of exposure to birds and hobbies were 4.24-fold and 3.58-fold higher in white individuals than in other races, which is an intriguing finding that, as the authors suggest, deserves further study.

The study also showed no substantial baseline differences in high-resolution CT findings or lung function between exposed and unexposed patients with ILD. Patients with any exposure had worse 2-year transplantation-free survival, but this was not significant after adjustment for the sex-age-physiology score and pack-years smoking. The stratification by baseline characteristics and the adjustments made to determine death risk helped lessen susceptibility bias. Yet, accepting that there is no relationship between exposed and unexposed patients with ILD and prognosis is premature when other differences have not been controlled for among cohort subjects, such as the point of time of inhaled exposures in the course of the disease and prior treatment.

By demonstrating that potentially relevant exposures are prevalent across ILD diagnoses, this study proves the feasibility of conducting population-based studies to estimate the population-attributable risk, which is a key measure of public health impact, of noninhalational ILDs other than IPF across a range of exposures or the expected reduction in ILD incidence if a particular exposure was removed.

This difficult-to-conduct much-needed investigation highlights one of the great challenges when considering whether an inhalational exposure may or may not be a risk factor for an ILD; the further down the causal chain, the more alternative explanations come into play. For instance, multiple end point adjustments as cleverly done by the investigators tend to cause loss of study power, making the probability of the detection of a true effect or association hard to find. Additionally, the authors correctly pointed out that having information on intensity, frequency, or duration of exposures would have helped demonstrate whether a dose-response relationship is present, thereby strengthening the argument between cumulative exposure and illness severity. This emphasizes the importance of a systematic approach to exposure assessment, both for research and in the clinic.

Looking forward, the study by Lee et al underscores the need to establish well-defined multicenter cohorts of patients with ILD with accurately characterized and quantified inhalational exposures to guide future clinical investigations and bench research. For example, the role of altered epigenetics in the pathogenesis of fibrotic and nonfibrotic ILDs could be characterized further from such cohorts. Harnessing this information is vital to understanding how to modulate the cumulative effects of environmental exposures and the associated biologic responses for preventive and therapeutic purposes in patients with ILD.

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References