Can united airway disease be the cause of variable severity experience of COVID-19 in health care workers?

Healthcare workers around the world are at high risk of exposure to the new coronavirus disease 2019 (COVID-19) infection because of the essential characteristics of their profession. Healthcare workers with COVID-19 account for 9–26% of all COVID-19 cases in European countries.[1-3] The World Health Organization reported that, during the severe acute respiratory syndrome (SARS) epidemic in 2002, the mortality rate among healthcare workers was confirmed to be 21%.[4] In 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is also a coronavirus, started to threaten the lives of healthcare workers like all humanity. Of the 1716 healthcare workers in China with confirmed COVID-19, 14.8% had the disease severe enough to be hospitalized, while 5 healthcare workers died due to COVID-19.[5]

According to the reports released by the International Amnesty Organization in March 2021, at least 17,000 healthcare workers all over the world have died due to COVID-19 within 14 months. And, with each passing day, the number of healthcare workers dying from COVID-19 is increasing.[6]

Various reasons such as working in high-risk departments, high viral load, long working hours, and the impaired immune system of individuals with high morbidity are among the hypotheses that try to explain why some healthcare workers suffer such severe COVID-19 infection and the clinical consequences are dire. However, thousands of healthcare workers without known immunological deficiency and risk factors lost their lives after being infected with the SARS-CoV-2 virus.[7] On the contrary, considering that some healthcare professionals working in the same clinic with similar characteristics were almost asymptomatic, it can be assumed that some other mechanisms affect this situation.

Until now, no definitive reason has been revealed as to why some of the healthcare workers experience severe COVID-19, while others experience mild enough to be asymptomatic. In this commentary, we want to discuss a new theory in terms of possible reasons why healthcare workers experience different severities of COVID-19 infection.

The upper and lower airways are assumed to be morphologically and functionally combined units. The link among them has been demonstrated by epidemiological, pathophysiological, and clinical evidence in health and disease.[8] This concept was first defined as the impact of the upper respiratory tract on the lower respiratory tract in the secondary centenary by Claudius Galenus in his study "De usu partium." Recently, the upper and lower respiratory tracts have been defined as a single, united airway.[9] And also, in the work of Claudius Galenus, the nose was described as a "breathing apparatus."

Located at the airway entrance, the nose defends the lower respiratory tract against the damage of inhaled air by performing effective ventilation. It also heats, cleans, and moisturizes the inhaled air so that the physiologically cleaned air, completely satisfied with watered gas at 37°C, is transported to the lungs.[9] Most molecules with the aerodynamic equivalent diameter > 15 μm accumulate in the upper respiratory tract if nasal breathing is performed. Molecules with aerodynamic equivalent diameters > 2.5 μm accumulate in the trachea and bronchi, while molecules with smaller aerodynamic equivalent diameters enter the gas transfer area of the bronchi.[10]

Bactericidal proteins like lysozyme, lactoferrin, antioxidants, and secretory IgA released from the rich submucosal glands in the nasal mucosa are involved in defending the lower respiratory tract against pathogens and allergens. In this way, it contributes to the effectiveness of both innate and acquired immune defenses. In contrast, during mouth breathing, cold and dry air causes bronchoconstriction where the nasal airways are bypassed, and the lower airways remain vulnerable to the ingress of allergens and pathogens.[9]

The co-occurrence of upper respiratory tract and lower respiratory tract disturbance is recognized as a united airway disease (UAD), which is defined as a single airway disease.[10] UAD is a mixed disturbance originated from allergic or non-allergic reproducible components and refers to the top-down continuity of inflammation in the common airway.[9] UAD, in which the allergic mechanism is effective, is related to allergic sensitization as evidenced by the existence of serum-specific immunoglobulin E (IgE) antibodies and/or positive skin tests. The causative agents may be any of the proteins of typical breathed-in allergens, such as house dust mites, animal hair, fungal spores, and pollen. The effect of the functioning of the upper respiratory tract on the functioning of the lower respiratory tract is particularly prominent in the allergic mechanism of UAD.[11]

Although the pathophysiology of allergic UAD is quite defined, the etiology and the structure of non-allergic UAD persist uncertain. Several possible mechanisms involve allergy provoked by unrecognized antigens (fungi), autoimmunity, and permanent infections sourced from Chlamydia trachomatis, Mycoplasma species, or viruses.[9] On the other hand, no IgE reactivity to allergens is observed in the non-allergic UAD phenotype. Meanwhile, the mechanisms of virus-induced UAD are still unclear and suggested hypotheses include epithelial injury or dysfunction, immunological responses, inflammatory mediator release, cholinergic and/or non-cholinergic reflexes, and impaired beta-adrenoceptor function.[11]

However, it is known that the two allergic and non-allergic UAD is related to an increased currency of rhinitis and asthma. Allergic rhinitis induced or exaggerated by allergic or non-allergic UAD is a chronic inflammatory disease of the upper respiratory tract. Rhinitis is actually a disease neglected by patients which is difficult to diagnose and overlooked by doctors.[9]

Allergic rhinitis is a clinical condition caused by mostly IgE-mediated immunological inflammation of the membrane of the nasal mucosa in which symptoms of nasal hypersensitivity occur. Typical causes that provoke allergy contain house dust mites, pollens, and fungi that occur in the environment, as well as organic or inorganic substances, to which a person has been exposed due to occupational exposure. These are mainly chemicals, blood and body fluids, enzymes, and vegetable proteins.[12] Although the prevalence of allergic rhinitis ranges from 26% to 33%, its incidence among healthcare workers is relatively high in relation to occupational exposure.[13]

Patients with atopic disease have a significantly increased risk of serious infections due to viruses and bacteria. Patients with mild or severe atopic disease are susceptible to both respiratory and non-respiratory microbial infections. For example, in adults, allergic rhinitis, atopic dermatitis, or both have been shown to increase the possibility of severe pneumococcal disease independent of asthma compared to those who do not have such conditions.[12] This is probably caused by the impairment of innate immunity in the respiratory tract and reduced humoral immune functions in patients with atopic disease. However, the molecular mechanism by which atopic conditions impairs immune functions and predisposes patients to microbial infections is unclear. Infections in these patients are probably not secondary to airway inflammation, but due to the immune dysfunctions, a potential

feature of atopic conditions, resulting in severe and widespread infections. While there are similarities across industries in terms of exposure to occupational allergens, the healthcare industry is unique in terms of occupational vulnerability to allergens, and therefore healthcare workers and other industrial workers should be evaluated separately when conducting occupational exposure research. Chemicals, cleaning materials, blood and body fluids, latex, aerosol medications, gases are among the main causes of allergy and irritation among healthcare workers.[14,15]

In this context, Laborde-Castérot et al.[16] reported that there were rhinitis and occupational asthma cases associated with ethylenediaminetetraacetic acid liquid sodium solutions in disinfectants verified by positive nasal provocation tests. It has been suggested that in the emergence of respiratory symptoms caused by ethylenediaminetetraacetic acid inhalation, allergic immune response or pharmacological mechanisms are more effective than irritant effects.[16] In addition, Adisesh et al.[17] emphasized that detergent enzymes should be considered to sensitize the respiratory tract. In addition, special attention has been paid to quaternary ammonium compounds in cases of occupational asthma after exposure to cleaners used in disinfection processes. It was demonstrated that exposure to these agents makes a 2-fold increase in the risk, whereas the use of protective gloves and masks reduces it.[18] In addition, occupational asthma due to exposure to powdered latex gloves, aerosol drugs, antibiotics, and local anesthetics has been reported in nurses, operating room workers, and pharmacists.[15]

Apart from these, frequent exposure to formaldehyde, ammonia, alcohol, quaternary ammonium compounds, and methylene diphenyl diisocyanate can induce occupational asthma in orthopedic plasters, while psyllium, pentamidine, and acrylates to which dentists are frequently exposed can also cause occupational asthma.[15]

Latex allergy is an important problem for healthcare workers. However, 75% of healthcare workers are unable to recognize the latex allergy that occurs in them. However, in another study, the probability of occurrence of at worst one sign due to the use of latex gloves in nurses was found to be 8.8%. In the same study, the presence of signs of glove dermatitis and type I latex allergy was detected in 77.1% of symptomatic nurses.[19] However, serological studies on latex allergy have revealed that the IgE enzyme-linked immunosorbent assay test has very low sensitivity. Therefore, it is impossible to detect all rhinitis cases caused by exposure to allergens using serological methods alone.

Laboratory employees are also exposed to a wide variety of chemical reagents when working. Histology technicians are subjected to stains, and pathologists are subjected to fixatives and preservative solutions. Operating room employees are exposed to anesthetic gases. Inhalation of chlorine, a widely used anesthetic gas, can cause irritation of the mucosal membrane of the lung, acute pneumonia, pulmonary edema, and transient bronchospasm.[14] Laser surgery and electro-cauterization with other high-energy devices may cause thermal degradation in tissues. Cooks and food service employees are subjected to grilling and frying smoke, nitrogen oxide, and gases used as fuel, thus becoming susceptible to allergic reactions.[14]

To our knowledge, there are no studies in the literature that show a direct relationship between the clinical consequences and prognosis of COVID-19 and atopic disturbances like allergic rhinitis, asthma, and atopic dermatitis.[20] Only one cohort study suggested that the presence of asthma and allergic rhinitis may be related to boosted infectivity of SARS-CoV-2, longer hospital stays, more ICU admissions, the need for more invasive ventilation, and higher mortality.[20] If there is a underlying allergic history, several possible pathophysiological mechanisms are thought to increase vulnerability to SARS-CoV-2 infection.[21]

Therefore, local immunological changes in the respiratory system are more likely to aggravate the infection involving the upper and lower respiratory tracts than systemic immunological changes.[20] Accordingly, viruses that affect the respiratory system enter the epithelium of the upper and lower respiratory tracts, making the bronchial defense system deteriorate. The mechanism of this deterioration is to trigger the local inflammatory cascades indicated by neutrophil uptake, T lymphocyte trafficking, and stimulation of resident monocytes.[21]

Viruses activate T helper type 2 pathways, causing the induction of cytokines such as interleukin (IL)-25 and IL-33 in epithelial cells, followed by eosinophilia, increased production of proinflammatory cytokines, such as IL-4, IL-5 and IL-13, and mucin production. As a result of all this, the symptoms get worse.[22]

In addition, the secretion of interferons (IFNs) such as IFN-I, IFN-III, which are normally produced in respiratory epithelial cells and mononuclear cells and are components of the innate immune system, is impaired in allergic individuals. These individuals become susceptible to viral infections.[21] Because these IFNs exert a critical role in stimulating the expression of genes that mediate the emergence of anti-viral effects by activating Janus/kinase signal transformers in bronchial epithelial cells and alveolar cells.[23]

Also, the expression of transmembrane serine protease 2, which is an entrance molecule for COVID-19, is higher in the nasal and airway epithelial cells of individuals with allergic rhinitis than in healthy individuals.[24] However, the COVID-19 infection that occurs in patients with non-allergic asthma is more severe than the COVID-19 infection that occurs in those with allergic asthma.[20] The possible mechanism for this interesting result is that the immune response that occurs due to non-allergic asthma is mainly driven by the T helper type 1 response and by the stimulation of neutrophils and mast cells. Since the immunological profile of patients with COVID-19 is polarized towards a classical T helper type 1 immune response, a more severe T helper type 1 immune response may occur in patients with non-allergic asthma.[20] However, as the potential adverse effects of not only T helper type 1 but also T helper type 2 responses on immunity are indicated in influenza virus, poliovirus, and human immunodeficiency virus infection, patients with allergic asthma have similar risk factors in terms of clinical consequences of COVID-19 as those with non-allergic asthma.

Based on this information, UAD, including allergic rhinitis and asthma, is very like to happen, especially in healthcare workers who are frequently exposed to occupational allergens. We believe that UAD caused by occupational allergens is a facilitating factor causing poor clinical outcomes of COVID-19 in healthcare workers.

Epidemiological studies detailing a positive association between atopy, allergic rhinitis, asthma, and UAD due to occupational exposure and the poor prognosis of COVID-19 in healthcare workers can help to understand the etiopathogenesis of COVID-19 and to find new treatment methods.

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References

1. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? *Lancet.* 2020;395:1225-1228.
2. Instituto de Salud Carlos III. Informe sobre la situación de COVID-19 en España. Informe COVID-19 nº 20. 3 de abril de 2020. https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Documents/INFORMES/Informes%20COVID-19/Informe%20n%c2%ba%2020.%20Situaci%c3%b3n%20de%20COVID-19%20en%20Espa%c3%b1a%20a%203%20de%20abril%20de%202020.pdf. Accessed by April 25, 2020.
3. International Council of Nurses. High proportion of healthcare workers with COVID-19 in Italy is a stark warning to the world: protecting nurses and their colleagues must be the number one priority. https://www.icn.ch/news/high-proportion-healthcare-workers-covid-19-italy-stark-warning-world-protecting-nurses-and. Accessed by April 25, 2020.
4. Chang D, Xu H, Rebaza A, Sharma L, Dela Cruz CS. Protecting healthcare workers from subclinical coronavirus infection. *Lancet Respir Med.* 2020;8:e13.
5. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323:1239-1242.
6. COVID-19: Health worker death toll rises to at least 17000 as organizations call for rapid vaccine rollout. https://www.amnesty.org/en/latest/news/2021/03/covid19-health-worker-death-toll-rises-to-at-least-17000-as-organizations-call-for-rapid-vaccine-rollout/. Accessed by March 5, 2021.
7. Ran L, Chen X, Wang Y, Wu W, Zhang L, Tan X. Risk factors of healthcare workers with coronavirus disease 2019: a retrospective cohort study in a designated hospital of Wuhan in China. *Clin Infect Dis*. 2020;71:2218-2221.
8. Ng K, Poon BH, Kiat Puar TH, et al. COVID-19 and the risk to health care workers: a case report. *Ann Intern Med*. 2020;172:766-767.
9. Licari A, Castagnoli R, Denicolò CF, Rossini L, Marseglia A, Marseglia GL. The nose and the lung: united airway disease? *Front Pediatr*. 2017;5:44.
10. Giavina-Bianchi P, Aun MV, Takejima P, Kalil J, Agondi RC. United airway disease: current perspectives. *J Asthma Allergy*. 2016;9:93-100.
11. Eccles C. Anatomy and physiology of the nose and control of nasal airflow. In: Adkinson NF, Bochner BS, Busse WW, Holgate ST, Lemanske R, Simons FER, eds. *Middleton's Allergy Principles and Practice.* 7th ed. Philadelphia: Elsevier; 2008:701-711.
12. Lambrecht BN, Hammad H. The immunology of asthma. *Nat Immunol.* 2015;16:45-56.
13. Scadding GK, Kariyawasam HH, Scadding G, et al. BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised Edition 2017; First edition 2007). *Clin Exp Allergy.* 2017;47:856-889.
14. Nathan RA, Meltzer EO, Derebery J, et al. The prevalence of nasal symptoms attributed to allergies in the United States: findings from the burden of rhinitis in an America survey. *Allergy Asthma Proc*. 2008;29:600-608.
15. Donnay C, Denis MA, Magis R, et al. Under-estimation of self-reported occupational exposure by questionnaire in hospital workers. *Occup Environ Med*. 2011;68:611-617.
16. Laborde-Castérot H, Villa AF, Rosenberg N, Dupont P, Lee HM, Garnier R. Occupational rhinitis and asthma due to EDTA-containing detergents or disinfectants. *Am J Ind Med.* 2012;55:677-682.
17. Adisesh A, Murphy E, Barber CM, Ayres JG. Occupational asthma and rhinitis due to detergent enzymes in healthcare. *Occup Med (Lond).* 2011;61:364-369.
18. Liss GM, Buyantseva L, Luce CE, Ribeiro M, Manno M, Tarlo SM. Work-related asthma in health care in Ontario. *Am J Ind Med*. 2011;54:278-284.
19. Liu QL, He XZ, Liang K, et al. Prevalence and risk factors for latex glove allergy among female clinical nurses: a multicenter questionnaire study in China. *Int J Occup Environ Health.* 2013;19:29-34.
20. Yang JM, Koh HY, Moon SY, et al. Allergic disorders and susceptibility to and severity of COVID-19: A nationwide cohort study. *J Allergy Clin Immunol.* 2020;146:790-798.
21. Edwards MR, Strong K, Cameron A, Walton RP, Jackson DJ, Johnston SL. Viral infections in allergy and immunology: How allergic inflammation influences viral infections and illness. *J Allergy Clin Immunol.* 2017;140:909-920.
22. Jackson DJ, Makrinioti H, Rana BM, et al. IL-33-dependent type 2 inflammation during rhinovirus-induced asthma exacerbations in vivo. *Am J Respir Crit Care Med.* 2014;190:1373-1382.
23. Contoli M, Message SD, Laza-Stanca V, et al. Role of deficient type III interferon-lambda production in asthma exacerbations. *Nat Med.* 2006;12:1023-1026.
24. Kimura H, Francisco D, Conway M, et al. Type 2 inflammation modulates ACE2 and TMPRSS2 in airway epithelial cells. *J Allergy Clin Immunol.* 2020;146:80-88.e8.

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