

## The elderly asthma pathogenesis is not as simple as we think

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Asthma in the elderly (AIE) usually refers to asthma in people aged 65 years and over. AIE is common and associated with higher rates and greater durations of hospitalization, more near-fatal attacks and greater mortality than asthma in younger patients.<sup>1</sup> The prevalence of current asthma in the elderly in the United States increased from 6.0% in 2001 to 8.1% in 2010.<sup>2</sup> The prevalence of asthma in the elderly Koreans was 12.7% and it was higher than that of developed countries.<sup>3</sup>

AIE is usually underdiagnosed, misdiagnosed, and frequently undertreated.<sup>4</sup> Comorbid diseases, impaired cognition and the psychosocial effects of aging can affect the diagnosis, clinical presentation and treatment of asthma in the elderly. Symptoms caused by asthma are frequently ignored or dismissed by older patients. Also, elderly patients, when compared with younger patients, have been shown to have a reduced perception of bronchoconstriction.<sup>5</sup> AIE might have a different pathophysiology than in childhood disease, resulting from complex interactions with various factors such as aging-related lung and immune alterations, epigenetic factors, environmental exposures, microbial triggers.<sup>6</sup>

Lung function of young and middle age asthmatics decline at a greater rate than normal subjects.<sup>7</sup> The rate of lung function decline accelerates with aging and smoking.<sup>7</sup> Airway obstruction was more marked in elderly asthmatics compared with healthy elderly or younger asthmatics.<sup>8</sup> Airflow obstruction in the older asthmatics may not be attributable to asthma alone. The pathologic changes of asthma may synergize with the changes of normal aging. The decline in lung function associated with aging is considered to result from loss of elastic recoil of the lung and reduced respiratory muscle strength. Aging and/or asthma duration can result in airway remodeling and cause “fixed” or irreversible airflow obstruction in the elderly.<sup>9</sup>

Changes in the aging immune system influence the airway inflammation in asthma in the elderly. Aging is associated with a chronic low grade inflammation called “inflammaging” characterized by increased Interleukin (IL)-1 $\beta$ , IL-6, and tumor necrosis factor- $\alpha$ .<sup>10</sup> In the elderly, asthma is more neutrophilic than in

younger asthmatics, whatever the severity of asthma.<sup>8,11</sup> Sputum neutrophilia can be found in older subjects without asthma as well.<sup>11</sup> This may be related to aging itself, extended exposure to environmental stimuli such as atmospheric pollution and environmental tobacco smoke.<sup>12</sup> The eosinophil effector function of degranulation and superoxide production were diminished in the older asthmatics compared with the younger asthmatics.<sup>13</sup> However, the clinical implications of these changes in the development of asthma in older patients remain unclear.

The Epidemiology and Natural History of Asthma (TENOR) study examined the natural history of elderly asthma compared with younger asthmatics and found that older asthmatics had lower total immunoglobulin E levels, fewer positive skin prick test responses, and less concomitant allergic rhinitis or atopic dermatitis.<sup>14</sup> When age of onset is considered, asthma with an early onset has a much higher association with positive allergy tests than late onset asthma. There is an emerging evidence of staphylococcal enterotoxin (SE) sensitization as a risk factor for adult asthma.<sup>15,16</sup> SE sensitization was significantly associated with smoking history and aging. *Staphylococcus aureus* is a frequent colonizer in the upper airway and skins, the airway epithelial disruption by repeated smoke exposure or reduced cutaneous barrier function by aging process could contribute to SE-IgE sensitization.<sup>16</sup> SE-IgE sensitization was significantly associated with late-onset asthma in the elderly, particularly severe eosinophilic asthma with chronic rhinosinusitis.<sup>17</sup>

Phenotyping of AIE have not been clearly established. There are at least two types of phenotype for AIE: long standing asthma (LSA) and late onset asthma (LOA).<sup>18,19</sup> Those with LSA have more atopy, severe airflow obstruction and less airway reversibility than those with LOA. AIE has many of the hallmarks of chronic obstructive pulmonary diseases (COPD) and patients with LOA are often misdiagnosed with COPD.<sup>20</sup> Recently, studies have been reported that classify clinical phenotypes of elderly asthma using cluster analysis.<sup>21,22</sup> However, current understanding for phenotypes of AIE is limited. Research is needed to identify the phenotypes and endotypes of elderly asthma for better diagnosis and treatment.

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