



Pulmonary disease and the autonomic nervous system: a new pathophysiological mechanism for Lady Windermere syndrome

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TO THE EDITOR:

Lady Windermere syndrome (LWS) is the eponym for a nodular bronchiocentric form of lung disease caused by nontuberculous mycobacteria (NTM) and occurring predominantly in tall thin White elderly women without previous lung disease. CT findings of LWS include centrilobular nodules, tree-in-bud opacities, and bronchiectasis. Lesions occur predominantly in the middle lobe and lingula (Figure 1). Although *Mycobacterium avium* complex is the most common causative agent, other species can cause LWS. The disease usually has a chronic course and an indolent behavior, as well as being characterized by a progressive increase in lesion size and number. Certain clinical and laboratory characteristics are more common in patients with LWS than in the general population, including scoliosis, pectus excavatum, mitral valve prolapse, benign joint hypermobility syndrome, and genetic mutations (related to cystic fibrosis, affecting ciliary function, causing connective tissue disorders, and involving immune function). Endocrine changes (such as reduced estrogen, leptin, and dehydroepiandrosterone, as well as increased adiponectin and cortisol) have also been reported. Most LWS patients are nonsmokers, and LWS can also affect men, albeit much less commonly. The mean age at diagnosis is usually higher in men than in women. Impaired bronchial clearance is part of the pathophysiological process. LWS is multifactorial, involving genetic, environmental, and aging-related factors.

Here, we hypothesize a pathophysiological mechanism for LWS based on knowledge of the physiology and pathophysiology of the autonomic nervous system, the aging process, and menopause. We suggest that changes in respiratory mechanics and autonomic dysfunction participate in the disease process, LWS occurring predominantly in women because of sex-specific autonomic differences, together with the effects of aging and menopause. A relative reduction in parasympathetic activity, as well as changes in lung and chest wall elasticity, together with a reduction in respiratory muscle strength, can predispose to NTM colonization and disease. Autonomic changes can reduce mucus production and modify the viscoelastic characteristics of the mucus, compromising airway smooth muscle function and cough reflex. Vagotomy significantly inhibits or suppresses cough reflex. Atropine and vagal blockade reduce basal tracheobronchial submucosal gland secretion. The fact that inhaled atropine slows mucociliary transport suggests that vagal tone influences secretion, clearance of tracheobronchial secretions, or both. The parasympathetic

nervous system also acts by locally regulating pulmonary inflammation and immunity.

Denervation generates hypersensitivity to stimuli, which is at least partially attributable to an increase in the number of receptors in the postsynaptic membrane. Methacholine acts on muscarinic receptors. In a study comparing asthma patients undergoing methacholine challenge testing, elderly patients had a greater reduction in FVC and a lower perception of bronchoconstriction than did younger patients.⁽¹⁾ In a study of COPD patients undergoing methacholine challenge testing, the prevalence of airway hyperresponsiveness was found to be higher in women than in men.⁽²⁾ These findings could be at least partially due to autonomic dysfunction. Systemic and local factors are associated with infections in lung transplant recipients, as well as with denervation. Among solid organ transplant recipients, NTM infection is most common in lung transplant recipients.

Differences in autonomic balance between men and women are related to female hormonal changes, autonomic changes also being related to aging. Alterations in extracellular matrix collagen can compromise autonomic activity. Many parasympathetic nerve fibers and almost all sympathetic nerve fibers touch effector cells or, in some cases, end up in the connective tissue adjacent to the cells to be stimulated. Acetylcholinesterase is linked to collagen and glycosaminoglycans in the local connective tissue. One study reported the interactions of acetylcholinesterase with collagen, sphingomyelin, and phosphatidylcholine.⁽³⁾ Differences in collagen turnover biomarkers have been reported between menopausal and premenopausal women, as well as between menopausal women and men.⁽⁴⁾ Other biochemical metabolites also change during menopause, including sphingomyelin (a component of the cell membrane, particularly nerve cells), leucine, and phosphatidylcholine.⁽⁵⁾ In a multicenter population-based study conducted in Europe, lung function (particularly FVC) was found to decline more rapidly in transitional and postmenopausal women, beyond the expected age change.⁽⁶⁾

Autonomic changes have been described in joint hypermobility syndrome, Ehlers-Danlos syndrome, and mitral valve prolapse syndrome. LWS can present with similar manifestations as these diseases.

Autonomic differences might be responsible for the difference between men and women with cystic fibrosis regarding average life expectancy, which is 2 years and 7 months shorter for women.^(7,8) This hypothesis is

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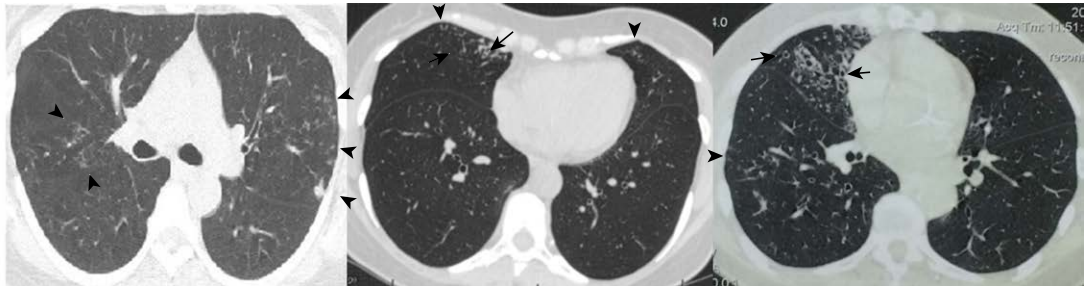


Figure 1. Common chest CT findings for Lady Windermere syndrome. Note centrilobular nodules with a linear branching pattern (tree-in-bud pattern; arrowheads) and bronchiectasis, the latter occurring predominantly in the middle lobe and lingula (arrows). The nodules in the middle of the secondary pulmonary lobule occur where the bronchioles are small in diameter, without cartilaginous support, and with relatively more developed musculature than that of the bronchi (an area theoretically subject to an earlier complication of neuromuscular damage).

consistent with the fact that, although women with cystic fibrosis undergo lung transplantation earlier than men, post-lung transplant survival is the same for men and women and independent of the gender of the donor.⁽⁷⁾ It is also of note that girls with cystic fibrosis have infections at a younger age than boys, and the difference in age at onset between males and females is greatest for NTM infections.⁽⁸⁾

Although COPD is associated with fibrocavitary NTM lung disease, most LWS patients are nonsmokers. Nicotine acts on nicotinic acetylcholine receptors. There are also differences between men and women regarding the effects of smoking on nicotinic acetylcholine receptors.⁽⁹⁾ A lack of nicotinic receptor stimulation might be associated with a predisposition to LWS.

In an animal study, nebulized hypertonic saline was reported to stimulate pulmonary vagal afferent

receptors.⁽¹⁰⁾ This could partially explain the therapeutic effect of nebulized hypertonic saline on humans infected with NTM.

The increase in the number of diagnosed cases of NTM lung disease in the world and the current therapy for this disease (long courses of antibiotics, resulting in side effects, resistance, and relapse) reinforce the need for new lines of research. Studies of the autonomic nervous and respiratory systems could provide a better understanding of the pathophysiological mechanism of LWS and have an impact on pulmonary and systemic conditions such as post-lung transplant follow-up, cystic fibrosis, smoking, and decline in lung function at menopause, as well as other diseases that behave differently in men and women, such as idiopathic pulmonary arterial hypertension and the COVID-19 inflammatory response.

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