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Pulmonary Disorders 2017: Serotonin receptor subtype-2 and idiopathic pulmonary fibrosis - Samah M Elaidy - Suez Canal University, Egypt

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Pulmonary fibrosis is a condition in which the lungs gradually become scarred. Symptoms include shortness of breath, dry cough, feeling tired, loss of weight and clubbing with the nails. Complications can include pulmonary hypertension, pneumothorax, respiratory failure and lung cancer. Causes include contaminants of the atmosphere, other drugs, diseases of the connective tissue, infections and interstitial lung diseases. The most severe is idiopathic pulmonary fibrosis (IPF), an unexplained cause of interstitial lung disease. Diagnosis can be based on symptoms, medical scans, biopsy of the lungs and tests of lung function. There is no proven cure. Treatment is targeted at symptom reduction measures, which can include oxygen therapy which pulmonary rehabilitation. Some medicines can be used to try to slow down the worsening of scarring. Lung transplantation can be an option on occasion. Around 5 million people worldwide are affected. Generally life expectancy is less than five years. Pulmonary fibrosis may be a side effect of certain illnesses. Most are classified as interstitial pulmonary diseases. Symptoms include autoimmune diseases, respiratory infections, and bacterial infection such as tuberculosis that may induce fibrotic changes in the upper or lower lobes of both lungs, and other microscopic lung injuries. Pulmonary fibrosis may, however, also occur without any known cause. In this case, "idiopathic" is called Most of the idiopathic cases are diagnosed as pulmonary idiopathic fibrosis. This diagnosis excludes a characteristic collection of histological / pathological features known as typical interstitial pneumonia. Pulmonary fibrosis involves the gradual exchange of normal fibrotic tissue parenchyma in the lungs. Replacing normal lung with scar tissue causes irreversible reduction in the oxygen diffusion capacity, and the resulting stiffness or reduced compliance makes pulmonary fibrosis a restrictive lung disease. Pulmonary fibrosis, rather than chronic inflammation, is perpetuated by aberrant wound healing. It is the primary cause of restrictive lung disease intrinsic to parenchyma in the lung. Quadriplegia and kyphosis, by contrast, are examples of causes of restrictive lung disease not necessarily involving pulmonary fibrosis. Lung biopsy can confirm diagnosis. Under general anesthesia, a videoscopically assisted thoracoscopic wedge biopsy (VATS) may be needed to obtain enough tissue to make an accurate diagnosis. This method of biopsy involves inserting multiple tubes through the chest wall, one of which is used to cut a piece of lung to be sent for examination. Histopathologic ally, the removed tissue is examined by microscopy to confirm the presence and pattern of fibrosis as well as the presence of other characteristics that may indicate a specific cause, e.g. specific types of mineral dust or possible therapy response, e.g. a pattern of so-called non-specific interstitial fibrosis. Misdiagnosis is common because, although overall pulmonary fibrosis is not uncommon, each particular form of pulmonary fibrosis is uncommon and patient assessment of these diseases is complex and involves a multidisciplinary approach. Terminology has been standardized but their application still presents difficulties. Even the experts may disagree with some cases being classified. Pulmonary fibrosis-induced hypoxia can lead to pulmonary hypertension, which, in effect, can lead to right ventricle heart failure. Oxygen supplementation can prevent hypoxia. Depending on these estimates, the prevalence of pulmonary fibrosis in the United States could range from over 29,000 to nearly 132,000 based on the population 18 years of age or older in the year 2000. Because of misdiagnosis the real figures may be considerably higher. Usually patients are diagnosed in their forties and fifties, although the occurrence of pulmonary idiopathic fibrosis rises significantly after age fifty. The loss of pulmonary function, however, is commonly attributed to old age, heart disease or more common lung diseases. Treatment options for pulmonary idiopathic fibrosis are extremely limited. Although research trials are ongoing, there is no evidence that any medication can help this condition

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significantly. Lung transplantation is the only therapeutic option available in severe cases. As certain types of lung fibrosis can react to corticosteroids. In the development of many forms of pulmonary fibrosis the immune system is felt to play a central role. Treatment with immune suppressive agents such as corticosteroids is aimed at reducing inflammation of the lung and subsequent scarring. Treatment answers are complex. Many whose symptoms improve with immune suppressive therapy presumably will not have idiopathic pulmonary fibrosis, as there is no effective treatment or cure for idiopathic pulmonary fibrosis. Two pharmacological agents intended to avoid scarring in moderate idiopathic fibrosis are pirfenidone, which decreased the rate of decline in FVC for one year. In the 6-minute walk study, pirfenidone also reduced the decrease in lengths, but had no effect on the respiratory symptoms. The second agent is nintedanib, which acts as an antifibrotic, mediated by inhibiting a number of receptors of tyrosine kinase (including platelet-derived growth factor, fibroblast growth factor, and endothelial vascular growth factor). A randomized clinical trial showed that it decreased deterioration in lung function and acute exacerbations.

Augmentation of lung serotonin (5-hydroxytryptamine, 5-HT) content is evident during development of pulmonary fibrosis with the implication of highly expressed metabotropic 5-HT2 receptors in the pathogenesis, ending in various mitogenic and profibrotic effects. In the fibrotic lung microenvironment, three 5-HT2 receptors subtypes- A, B, C- are recognized. The 5-HT2A and 5-HT2B receptors are chiefly confined to fibroblasts, alveolar epithelial cells, with an augmented allocation of 5-HT2C receptors into alveolar macrophages. These unique allocations allow multiple intersecting serotonergic pathways, which modulate different fibroproliferative and angiogenic key regulators in fibrotic lung microenvironment. Recently in lung fibrosis, 5-HT2C has been found to play a major phenotypical alternating role on alveolar macrophage with subsequent progression into inflammatory-fibrotic cascades. In several recent studies, selective specified pharmacological antagonism of 5-HT2A and/or 2B and/or 2C receptors was found to attenuate bleomycin-induced lung injury and fibrosis through improving lung functions, decreasing lung edema and down regulating several collagen deposition mediators, as tumor necrosis factor-α (TNF-α), transforming growth factor-β1 (TGF-β1), connective tissue growth factors (CTGF), plasminogen activator inhibitor-1 (PAI-1), monocyte chemo attractant protein-1 (MAP-1) and vascular endothelial growth factor (VEGF). In conclusion, blockade of 5-HT2A, 2B, and 2C receptors is considered a promising molecular target for pharmacological intervention in fibro-proliferative interstitial lung diseases. However, further studies are needed to explore in depth the complexity of roles played by different 5-HT2 receptor subtypes and the therapeutic implications of antagonizing their effects in idiopathic pulmonary fibrosis.

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