



Dementia in patients with chronic obstructive pulmonary disease

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Abstract

Chronic obstructive pulmonary disease (COPD) and dementia are both extremely widespread chronic diseases with a significant impact on world health. The most common comorbidity of COPD is dementia, leading to an increased need for hospitalization, difficulties with daily functioning, an increased need for care services, and rate of mortality. 4% and 61% of patients with COPD reported developing cognitive impairment. Alteration in cerebral perfusion in patients with COPD results from hypoxemia, which is an abnormal decrease in oxygen in the blood, and these changes contribute to the development of cognitive decline. Long-term hypoxia, hypercapnia, and increased inflammatory cytokines in COPD patients contribute to the development of degenerative brain diseases (including structural changes in the brain and reduced white matter integrity). Psychomotor speed, planning, verbal memory, and cognitive flexibility are cognitive domains affected in patients with COPD. The risk of dementia increases with age but is unaffected by gender.

Keywords: Chronic obstructive pulmonary disease, Dementia, Pathophysiology

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Introduction

COPD is a chronic pulmonary disease associated with cognitive impairment in the elderly. Chronic obstructive pulmonary disease COPD is a chronic pulmonary and heterogeneous disorder.⁽¹⁾ 380 million people all over the world are affected by COPD, which causes an increase in mortality rates, healthcare needs, and impaired quality of life.⁽²⁾ In 2019, low- and middle-income countries reported 3 million deaths caused by COPD.⁽³⁾ In 2019, the number of patients suffering from COPD worldwide reached 212.3 million. 5.4 million people will die from COPD by; 2060⁽⁴⁾ It is a lung disease that typically onsets after the age of 55, causing breathing problems and chronic, partially irreversible obstruction of airflow.⁽⁵⁾ Prolonged exposure to toxic gases and cigarette smoke causes

lung-related inflammatory conditions called chronic obstructive pulmonary disease.⁽⁶⁾

The pathophysiology of the disease includes inflammation of the airways, lung parenchyma, and pulmonary vasculature. Inflammatory cells, including neutrophils and macrophages, release several inflammatory mediators, which lead to the destruction of alveolar air sacs with oxidants and excess proteases. The inflammatory response leads to the destruction of alveolar air sacs, tissue damage, airway obstruction, and impaired gas exchange that causes a decrease in the forced expiratory volume (FEV1). Emphysema occurs due to the destruction of the alveolar air sacs, which are the (gas-exchanging surfaces of the lungs). In emphysema, an irritant (e.g., smoking) causes an inflammatory response,

oxidative stress, and protease-ant protease imbalances. During exhalation, airway collapse is a result of damage to the elastic recoil that is destroyed by excess proteases.⁽⁷⁾ In addition to protease-antiprotease imbalances, emphysema may also occur due to an Alpha-1 antitrypsin deficiency. Misfolding of mutant protein in the liver can lead to Alpha-1 so COPD patients with liver damage are expected to have AATD. The most common site of AATD in a patient with smoking-related emphysema is the lower lung lobe.⁽⁸⁾ Radiographic imaging shows hyperinflation of the lungs during exhalation due to airway collapse and air trapping. An increase in carbon dioxide (CO₂) is characteristic of this disease due to the impairment of gas exchange and the inability to fully exhale. As the disease progresses with a reduction in ventilation, diffuse hypoxemia and CO₂ retention lead to vasoconstriction and pulmonary hypertension.⁽⁹⁾ Persistent cough, breathlessness, and irreversible airflow limitation are critical symptoms of COPD.⁽¹⁰⁾ Exacerbation in COPD patients is usually triggered by exposure to harmful microbes, like bacteria and viruses, in the environment.⁽¹¹⁾ Comorbidities of COPD may have a significant impact on the disease course, quality of life, and economic cost of the disease.⁽¹²⁾ Ischemic heart disease, hypertension, diabetes, and lung cancer are common comorbidities associated with COPD.⁽¹³⁾ COPD has different extra pulmonary complications such as osteoporosis, metabolic syndrome, diabetes, cognitive impairment (CI), etc. and is considered the third leading cause of death.⁽¹⁴⁾ COPD can be treated if detected in the early stages and is preventable. The strategy for the management of COPD must include the avoidance of the risk of exacerbation and symptomatic treatment.⁽¹⁵⁾ Pharmacotherapy, cessation of smoking, pulmonary rehabilitation, and continuous monitoring of disease progression are the main factors of COPD management.⁽¹⁶⁾ The main aim of treatment is to improve the quality of life decrease the risk of exacerbation, mortality and control symptoms. Treatment options include pharmacological and non-pharmacological approaches, including smoking cessation and pulmonary rehabilitation.⁽¹⁷⁾ Pharmacological treatment of COPD is restricted to bronchodilators (beta2-agonists, antimuscarinics and methylxanthines) and anti-inflammatory drugs like corticosteroids, inhaled corticosteroids (ICS), systemic glucocorticoids, phosphodiesterase-4

(PDE4) inhibitors, and antibiotics.⁽¹⁸⁾ All COPD patients are recommended to receive Influenza vaccination annually. Patients aged 65 and over should receive the 13-valent pneumococcal conjugate vaccine and the 23-valent pneumococcal polysaccharide vaccine is recommended for COPD patients especially those aged 65 at least one year apart. COPD patients with comorbidities (e.g., diabetes mellitus, chronic heart disease, and chronic lung disease) are recommended to receive the 23-valent pneumococcal polysaccharide vaccine.⁽¹⁹⁾ According to the severity of the exacerbations of COPD, the patient can be managed, outpatient or inpatient. The severity of exacerbation is classified by the presence of worsening dyspnea, sputum volume, and purulence. Mild exacerbations need outpatient management with bronchodilators, corticosteroids, and antibiotics. Moderate and severe exacerbations need hospitalization and patients often require oxygen and bronchodilator therapy in the form of a short-acting beta2-agonist with or without short-acting antimuscarinic agents. When the patient becomes stable, long-acting bronchodilators are used. Oral corticosteroids are more effective, with fewer side effects than intravenous corticosteroids. If bacterial infection is suspected, antibiotics are recommended. In moderate to severe cases oxygen therapy is recommended and can range from a nasal cannula to mechanical ventilation.⁽²⁰⁾

Dementia

Dementia is considered a global health problem, as the number of cases is projected to increase from around 57 million to 152 million by 2050.⁽²¹⁾ The number of cases of dementia nowadays is 35.6 million as reported by The World Health Organization but this is estimated to increase over the next 20 years .5 to 10% of patients with Mild Cognitive Impairment (MCI) annually will be converted to dementia.⁽²²⁾ 0.8 to 27% of deaths caused by dementia have been reported worldwide.⁽²³⁾

Dementia is a broad term that include impairment in different cognitive domains including the process of information handling, attention and concentration, memory, executive functioning and self-control.⁽²⁴⁾ Dementia refers to a brain function syndrome that is significant enough to interfere with daily activities while Mild Cognitive Impairment (MCI) refers to a syndrome involving the onset of

age and education related cognitive impairments that are not significant enough to interfere with daily activities.⁽²⁵⁾ Risk factors for dementia include smoking, diabetes, and body mass index. COPD, a common disease in the elderly population, has also been found to be a risk factor for cognitive decline.⁽²⁶⁾ Alzheimer's disease (AD) is the most common type of dementia and neurodegenerative disorders followed by Parkinson disease (PD). Other type of dementia following Alzheimer's include vascular dementia, dementia with Lewy bodies, frontotemporal dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, Huntington's Disease, and mixed dementia.⁽²⁷⁾ AD and PD are neurocognitive disorders in which inflammatory cytokines have the main role in the pathogenesis of degenerative processes. Inflammation is considered a marker for both immunological response and tissue damage, and may occur after tissue damage in many diseases particularly neurodegenerative diseases.⁽²⁸⁾ Not all cases of MCI will develop dementia, and MCI can be reversible in some cases. Several researches have great interest in predictors for the progression of MCI to dementia and modifiable risk factors. Although the diagnosis of MCI mustn't be associated with a comorbid condition, this approach found that 50% of those with MCI have a medical co-morbidity.⁽²⁹⁾ Dementia is a leading cause of death and disability worldwide among the elderly, following cancer, heart disease, and cerebrovascular disease.⁽³⁰⁾ Primary prevention therapy for dementia aims to reduce the risk of development, while early intervention therapy aims to slow the progression of the disease. A good understanding of the risk factors of dementia, such as cardiovascular risk factors, can improve the therapeutic interventions and health outcomes of dementia patients.⁽³¹⁾

Relationship between COPD and dementia

There are several studies that suggest a relationship between COPD and the development of dementia. In 1982, the first report was published on dementia in COPD patients.⁽³²⁾ 5.5% of adults with COPD show dementia measured using the Mini-Mental State Examination (MMSE), the prevalence rate of cognitive impairment measured with multiple cognitive tests is up to 77.0% in patients with both COPD and hypoxemia.⁽³³⁾ COPD patients usually show mild or subclinical cognitive decline so it may

not contribute to the overall pathology of the disease.⁽³⁴⁾

Pathophysiology

Cerebral hypoxemia, atrophy of the hippocampal, and release of inflammatory mediator that lead to damage of neuron are involved in the hypothesis of cognitive dysfunction.⁽³⁵⁾ Structural changes due to long-term hypoxia, hypercapnia, and increased inflammatory cytokines in COPD patients contribute to the development of degenerative brain diseases (including structural changes in the brain and reduced white matter integrity).⁽³⁶⁾ Chronic systemic inflammation and increased inflammatory cytokines in patients with COPD cause neuronal damage and lead to neurodegeneration and development of dementia.⁽³⁷⁾ Local and systemic inflammation result in cellular defects and further increasing damage in pulmonary and vascular diseases activate microglial cells in the brain which may develop in response to smoking, as with aging.⁽³⁸⁾ Aging lead to the chronic increase in glucocorticoid level and hippocampus loss ability to control release of glucocorticoid by the thalamus, which exposes the body systems to elevated stress hormone concentrations.⁽³⁹⁾ Hypoxemia result in brain tissue break down, myelin damage and increased turnover of neuronal membrane precursors due to increase in brain choline concentration.⁽⁴⁰⁾ In particular, patients with COPD may show cerebral perfusion alterations as a consequence of hypoxemia, which is an abnormal decrease in oxygen in the blood, and these changes contribute to cognitive decline. Hypoxia can alter neuronal cell dysregulation and neuroinflammation.⁽⁴¹⁾ The brain has a mechanism to respond to hypoxemia called cerebrovascular oxygen reactivity, which counteracts cerebral hypoxemia by increasing blood flow by up to 200% in conditions of oxygen desaturation during chronic nocturnal hypoxemia or induced by exercise. Studies have found that cerebral blood flow is much higher in hypoxemic COPD patients than in non-hypoxemic patients.⁽⁴²⁾ There is no cerebral hypoxemia during rapid eye movement (REM) sleep in COPD patients, while during non-rapid eye movement (NREM) sleep, cerebrovascular oxygen reactivity is missing.⁽⁴³⁾ 38–70% of non-hypoxemic COPD patients show nocturnal desaturation.⁽⁴⁴⁾ When the mechanisms of response of the brain to hypoxemia are inoperative, injury to the central nervous

system (CNS) will occur due to the effect of nighttime desaturation. 50% of non-hypoxemic COPD patients show no cerebrovascular reactivity mechanism which leads to brain injury formation during NREM sleep desaturations.⁽⁴⁵⁾

Risk factors for Dementia

several factors thought to increase the risk of dementia in COPD patients include smoking, aging, physical inactivity, inflammation, atherosclerosis, cardiovascular disease, hypertension, diabetes, BMI, hypoxemia, hypercapnia, and obstructive sleep apnea.⁽⁴⁶⁾ Poor quality of life, living alone, female sex, smoking and low socioeconomic status are factors associated with the severity of the disease in COPD patients and psychological constructs that can lead to an increased level of anxiety and depression in those patients.⁽⁴⁷⁾ There is limited evidence for a significant effect of the treatment of COPD on cognitive function.⁽⁴⁸⁾ Long-term use of inhaled corticosteroids, antibiotics, and the bronchodilator-related "anticholinergic burden, might induce cognitive decline, as reported by some previous studies.⁽⁴⁹⁾ In the first year of treatment, 50% of patient with COPD don't follow the prescribed inhaled medication and only 25% use oxygen therapy for outside activities as reported by several previous studies.⁽⁵⁰⁾ Older patients and those with dementia also don't follow the prescribed inhaled therapy. Those patient are unable to recall how and when to use oxygen therapy and the inhaler devices. Cognitive impairment in those patients has a negative impact on the compliance of the treatment.⁽⁵¹⁾ Isolation, depression, lack of pulmonary rehabilitation and muscular dysfunction programs developed by COPD patients increase the incidence of dementia among the COPD population.⁽⁵²⁾

The cognitive domains

Cognitive processes are formed of different cognitive domains including learning, visuospatial attention, concentration, language, and executive functions.⁽⁵³⁾ Cognitive domains impaired in people with COPD differ from those affected in those diagnosed with Alzheimer's dementia or other types of dementia as reported by several studies.⁽⁵⁴⁾ Problem solving, decision making, language, and cognitive flexibility are domains affected in patients with COPD after correction for comorbidities.⁽⁵⁵⁾ Attention, executive functioning, (visual) memory, problem-solving, concentration, logical and abstract reasoni-

ng, planning, coordination, and organization are also impaired in patients with COPD.⁽⁵⁶⁾ The degree and pattern of impairment in different cognitive domains is diffuse and differs from one patient to another.⁽⁵⁷⁾ The pattern of cognitive impairment in COPD is diffuse, This pattern resembles aging-related cognitive deterioration as a manifestation of accelerated aging.⁽⁵⁸⁾ This would be clinically relevant for the management of COPD patients with cognitive impairment and for the care of their comorbid disease, as specific types of cognitive impairment may have different management strategies.⁽⁵⁹⁾

Diagnosis of dementia in patients with COPD

Computed tomography (CT) scan and magnetic resonance imaging (MRI) can be used for the assessment of the neuroanatomical of brain structures and their function. they can also exclude brain pathology as strokes, brain tumors or vascular malformation.⁽⁶⁰⁾ Brain lesions are widely distributed and show loss of grey matter in the precuneus, right inferior parietal lobule, right superior temporal gyrus/middle temporal gyrus, hippocampus, limbic and paralimbic structures, cingulate, amygdala as reported by several studies using MRI which explain the broad neurologic manifestations in these patients.⁽⁶¹⁾ For research the fluorodeoxyglucose positron-emission tomography (FDG-PET) scan can be used and more accurate and sensitive than MRI in MCI diagnosis for assessment of brain function. Highly active brain areas can be detected by (FDG-PET) that uses a radioactive glucose tracer which binds to these areas. The presence of hypometabolic areas in the temporal or parietal lobe increase the risk that patient with MCI will develop dementia as it is a sign of neurodegeneration.⁽⁶²⁾ An increase of frontal lobes choline (which is a reliable marker of myelin destruction with alteration of neuronal membrane turnover) is shown as white matter hyperintensities on MRI as the result of brain damage in severe COPD hypoxemic patients due to desaturations during the effort in daily activities.⁽⁶³⁾ The pattern of vascular brain disease seen in COPD can be explained by cardiovascular risk and smoking alone and is different from that of ischemic cerebrovascular disease and vascular dementia.⁽⁶⁴⁾ Cognitive domains, such as episodic memory, executive function, and language have been found to be impaired

in COPD patients while the pattern of impairment in vascular dementia shows lower scores in attention, memory and fluency.⁽⁶⁵⁾ White matter damage not only seen in advanced cases of COPD but also in stable non hypoxemic patients with COPD.⁽⁶⁶⁾ Clusterin is a plasma biomarker seen in patient with dementia in the elderly and in advanced cases of COPD and is considered a mediator of the relationship between COPD and dementia.⁽⁶⁷⁾

Assessment of dementia

The use of multiple diagnostic tests may improve the detection of cognitive deficits include the MMSE, other diagnostic tests that have demonstrated utility include the Montreal Cognitive Assessment test, the Trail Making Test, tactical performance tests, the Wechsler Adult Intelligence Scale, immediate and delayed verbal and nonverbal memory tests and the Alzheimer's Disease Assessment Scale-Cognitive subscale.⁽⁶⁸⁾ Electroencephalography utilizing both auditory and visual P300-evoked responses has revealed that progressive impairment of the auditory (but not visual) P300 reaction time occurs with increasing severity of COPD.⁽⁶⁹⁾

Treatment options for dementia in COPD patients

Psychological difficulties that negatively impact treatment adherence and self-management so that Cognitive behavioral therapy or psychological support should be considered. Previous studies reported that the use of long-term oxygen therapy (LTOT) decrease the risk of dementia among the COPD population.⁽⁷⁰⁾ Treatment with Donepezil plus memantine versus donepezil alone could stabilize or slow declines in cognition and function, based on the results of prior studies.⁽⁷¹⁾ Increase physical activity has a positive impact cognition in patients with COPD as decreasing oxidative stress, reducing systemic inflammation, and improving microvascular circulation.⁽⁷²⁾ Social isolation, anxiety, and depression result from reduced mobility may also contribute to progressive cognitive impairment. Exercise programs to improve cognition have been studied.⁽⁷³⁾

Impact of dementia on disease management in COPD

Dementia in COPD patients can affect the disease management and cause worse. During treatment of

COPD patients they must learn inhaler technique, as well as to organize, and execute self-care functions⁽⁷⁴⁾. Increased risk of sepsis, respiratory failure and mortality in patient with cognitive impairment and COPD.⁽⁷⁵⁾ Impaired lung function in communities study was associated with atherosclerosis, poor cognitive performance, and an increased risk of dementia hospitalization.⁽⁷⁶⁾ Dementia in patients with COPD contributing to impairment with daily functioning, an increased need for hospitalization and mortality, and an increased need for care services.⁽⁷⁷⁾

Conclusions

There is a relationship between COPD and the development of dementia. 5.5% of adults with COPD show cognitive impairment measured with the Mini-Mental State Examination (MMSE), and the prevalence rate of cognitive impairment measured with multiple cognitive tests is up to 77.0% in patients with both COPD and hypoxemia. Proposed causal mechanisms include hypoxia-mediated neuronal damage or a reduction in neurotransmitters that require oxygen-dependent enzymes for synthesis. Several neuroimaging studies suggest that cerebral white matter lesions in patients with COPD have a greater link with anxiety and depression rather than significant cognitive impairment. Long-term hypoxia, hypercapnia, and increased inflammatory cytokines in COPD patients contribute to the development of degenerative brain diseases (including structural changes in the brain and reduced white matter integrity). Dementia is considered a common comorbidity in patients with COPD, contributing to adverse factors such as difficulties with daily functioning, an increased risk of hospitalization and mortality, and an increased need for care services. Patient with chronic diseases as COPD patients should be assessed for their cognitive abilities regularly to guard against dementia that impair self-management, adherence and personal independence. Psychological factors including depression and anxiety can affect adherence to rehabilitation programs and management of COPD. There is an increased risk of sepsis, respiratory failure and mortality in patient with cognitive impairment and COPD.

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