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Review article

Chronic obstructive pulmonary disease and cerebrovascular disease: A comprehensive review

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ABSTRACT

Along with the aging population, the public health burden of cerebrovascular disease is increasing. Cerebral small vessel disease and accumulation of brain pathology associate with cognitive decline and can lead to clinical outcomes, such as stroke and dementia. Chronic Obstructive Pulmonary Disease (COPD) is a common respiratory disease among elderly. The quality of life and prognosis of patients with COPD is greatly determined by the presence of comorbidities including stroke and cognitive impairment. Despite the clinical relevance of cerebral small vessel disease, stroke and (vascular) cognitive impairment in patients with COPD, literature is scarce and underlying mechanisms are unknown.

The aim of the present review is therefore to summarize current scientific knowledge, to provide a better understanding of the interplay between COPD and the aging brain and to define remaining knowledge gaps.

This narrative review article 1) overviews the epidemiology of cerebral small vessel disease, stroke and cognitive impairment in patients with COPD; 2) discusses potential underlying mechanisms including aging, smoking, systemic inflammation, vasculopathy, hypoxia and genetic susceptibility; and 3) highlights areas requiring further research.

Contents

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1. Introduction

The main task of the lungs is to provide oxygen to the blood and eliminate carbon dioxide from the blood. 20% of the total body oxygen is consumed by the brain [1]. Inevitably, impairment of the lungs will affect structure and functioning of the brain. Particularly elderly are prone to a distorted supply of oxygen to the brains. Aging of the brain mainly affects high metabolic demanding neurons and the brain reserve capacity is reduced in elderly [2,3]. By focusing on mortality rates rather than disability rates, the large burden of neurological disorders has been underestimated in Europe [4]. Increasing evidence demonstrates that cerebral vessel disease and accumulation of brain pathology associate with cognitive decline and can lead to clinical outcomes, such as stroke and dementia. However, a large part of neurological diseases remains subclinical and may lead to subtle deficits, only measurable with cognitive testing and visualized with magnetic resonance imaging (MRI).

Worldwide, Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of mortality, and the overall severity and prognosis of patients with COPD is strongly influenced by associated concomitant diseases [5,6]. Stroke and cognitive impairment have been described to be more prevalent in patients with COPD [7–9]. With the increasing recognition that COPD extends beyond the lungs, particular interest grows to study lung–brain interactions.

In this narrative review article, we provide a general overview of the link between cerebrovascular disease and COPD, including the epidemiology, pathophysiology and impact of cerebral small vessel disease, stroke and cognitive impairment. We performed a title search combining COPD search items with cerebrovascular disease, stroke, cerebral small vessel disease and cognitive impairment. Further in this review, we describe potential underlying mechanisms -adding novel markers of cerebral small vessel disease- and we summarize the impact of aging and smoking on the association between COPD and cerebrovascular disease. Finally, we address the current knowledge gaps and indicate potential future research directions.

2. Epidemiology

2.1. Cerebral small vessel disease

Cerebral small vessel disease refers to pathological processes affecting small arteries, arterioles, venules and capillaries of the brain which are etiologically related to cerebral amyloid angiopathy or hypertensive/arteriolosclerotic microangiopathy [10]. Cerebral small-vessel disease is common among elderly, and Magnetic resonance imaging (MRI) is used to visualize effects of small vessel disease [10–12]. Among the MRI markers, we can distinguish: A. focal markers, such as white matter lesions, lacunar infarcts, and microbleeds (brain parenchyma lesions); B. atrophy markers, such as brain atrophy/lobar atrophy/hippocampus atrophy and C. emerging markers, such as diffusion tensor imaging (microstructural integrity) or amyloid imaging (using positron emission tomography [PET] tracers that bind to amyloid plaques). In addition, MRI can also be used to quantify total brain perfusion (e.g. phase-contrast MRI) or regional perfusion (e.g. arterial spin labeling).

Cerebral small-vessel disease plays an important role in cerebrovascular disease and age-related cognitive decline and functional disability [10–12]. Regarding associations with the lung, elderly subjects with impaired pulmonary function (measured by FEV_1) have decreased regional white matter volume in the cerebellum and a higher prevalence of subclinical cerebral infarctions and white matter lesions [13,14].(Table 1) Moreover, recent evidence has linked COPD to cerebral small vessel disease through an increased presence of cerebral white matter lesions [15,16] and a higher prevalence of cerebral microbleeds (45% in COPD subjects compared to 31% in controls without COPD) [17].(Table 1)

Furthermore, COPD would preferentially lead to the development of deep or infratentorial microbleeds which are thought to occur by arteriolosclerosis on the basis of hypertensive vasculopathy and lipohyalinosis [11,17]. The risk on deep or infratentorial microbleeds increased with severity of airflow limitation, dyspnea symptoms and exacerbations [17]. The chronic bronchitis phenotype seemed to have less influence although numbers of COPD subjects conferring this phenotype were low [17]. Because small vessel disease can lead to thrombosis and subsequent stroke due to lipohyalinosis, fibrinoid degeneration or atheroma formation, small vessel disease may be partially responsible for the observed increased stroke risk in patients with COPD. Microbleeds occurring in strictly lobar brain sites which are indicative of cerebral amyloid angiopathy, were not differentially affected, suggesting that COPD might be less involved in beta-amyloid pathology, which underlies Alzheimer's dementia [11,17,18]. However, acknowledging the paucity in current evidence, more research is needed to evaluate the impact of cerebral small-vessel disease on stroke and cognitive functioning in patients with COPD.

2.2. Stroke

Stroke is one of the most common neurological diseases worldwide. Since 2010, stroke is the second leading cause of death globally [6]. A stroke is defined according to the World Health Organization (WHO) as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 h or leading to death, with no apparent cause other than that of vascular origin.” [19] The underlying cause can be a blockage in one of the blood vessels supplying the brain of oxygen and nutrients, called an ischemic stroke, or a weakened or ruptured brain vessel causing bleeding in (intracerebral) or around (subarachnoidal) the brain, called a hemorrhagic stroke. Ischemic strokes are further subtyped into large vessel stroke, small vessel stroke and cardioembolic stroke and they are mainly caused by atherosclerotic disease, cerebral hypoperfusion and cardiac embolism. A transient ischemic attack (TIA) is defined as a brief and transient episode of neurological dysfunction caused by focal temporary cerebral ischemia without cerebral infarction [20]. TIAs are associated with full neurological recovery and clinical symptoms typically last less than 1 h [20].

Table 2 summarizes the increasing evidence relating impaired pulmonary function (measured by the Forced Expiratory Volume in 1 s [FEV_1]) to stroke and stroke-associated mortality [21–26]. Prevalence figures for any stroke in patients with COPD ranged from 4.8 to 9.9% with the highest percentages observed in the youngest populations [9,27–29].(Table 2) Only one study evaluated the influence of the severity of airflow limitation on stroke in subjects with COPD and observed slightly higher effect estimates in COPD subjects with mild airflow limitation [28].(Table 2) As described in the previous section, the increased presence of cerebral small vessel disease in patients with COPD might increase the risk of hemorrhagic strokes. In addition, recent studies have shown that carotid arterial plaque burden is increased in patients with COPD and that these plaques are more prone to rupture, due to an increased lipid content, potentially leading to ischemic strokes [30–32]. However, longitudinal studies well-controlled for the potential confounders are needed to accurately define the increased risk of stroke and the different stroke subtypes in patients with COPD.

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