Chronic Obstructive Pulmonary Disease

Chapter 1

Cognitive Impairment in Chronic Obstructive Pulmonary Disease: A Multifactorial Problem Screaming for Attention

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Abstract

Cognitive impairment in patients with Chronic Obstructive Pulmonary Disease (COPD) is a prevalent symptom with detrimental consequences on many aspects of patients` functioning and health status, as well as it may affect the course of respiratory treatment. COPD pathology seems to be accountable for the high prevalence of cognitive impairment in those patients. It includes several determinants of cognitive impairment which present a potential independent and overlapping impact on cognitive function in COPD. Hypoxia and systemic effects of COPD are common risk factors for the development of cognitive deficits. Early detection of cognitive impairment in COPD patients is crucial in order to prevent, delay or even treat the progress of cognitive decline. Pulmonary rehabilitation as comprehensive therapeutic intervention can provide opportunities to attenuate cognitive decline in COPD.

Keywords: Cognitive Dysfunction; Cognitive Deficits; Comorbidities; Extrapulmonary Effects; Respiratory Treatment; Pulmonary Rehabilitation; Chronic Obstructive Pulmonary Disease.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a gradually progressive condition associated with pulmonary and systemic inflammation as well as numerous extrapulmonary-consequences [1,2]. A common systemic effect in COPD is the cognitive impairment which could be defined as confusion or memory loss beyond what is expected in normal ageing. Although cognitive impairment is not limited to a specific age group, older individuals are more vulnerable to cognitive deterioration [3,4]. Next to ageing which is the source of pri-

mal vulnerability for cognitive impairment in all individuals, COPD-related pathophysiology can increase even more the risk for steeper cognitive decline in patients with COPD [5,6]. Indeed, plethora of evidences has demonstrated a relationship between cognitive impairment and COPD manifestation [7,8].

The prevalence estimates of cognitive impairment have an average range of 36% amongst patients with COPD, where as only a 12% amongst individuals of general population present evidences of cognitive impairment [9]. Hung and colleagues [5] analyzed a large population-based longitudinal cohort of 4,150 individuals and reported that cognition scores of older adults with both severe and non-severe COPD were significantly lower when compared to adults without COPD (2.6 points [$P < 0.001$] and 0.9 points [$P < 0.001$], respectively [5]. Moreover, Singh and colleagues [10] using a large cohort of subjects reported that COPD patients are twice as likely to develop mild cognitive impairment characterized by increased memory loss than controls while the risk was higher among those who have had the lung disease for a long time [10]. Those evidences indicate an association between impaired lung-function and brain pathology that seems to be undisputable.

A comprehensive non-systematic review of the literature to explore a link between COPD and the occurrence of cognitive impairment has been performed taking into account insights from genetic, molecular, neuropsychological and COPD studies. The main hypothesis is that cognitive impairment is prevalent in COPD patients and attributed to several COPD-related pathological consequences. This review introduces cognitive impairments as a prevalent symptom in COPD and summarises the evidences of an association between COPD pathology and cognitive impairment. Moreover, it examines the burden of cognitive impairment in COPD and investigates potential beneficial effects of Pulmonary Rehabilitation on patients with cognitive deficits.

2. Cognition and Neuropsychological Domains

Cognition is defined as “the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses” indicating a range of mental processes that occur when people receive a new information and the way that human behavior can be adapted to new situations and/or preferences changes [11,12]. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [13] defines six basic domains of cognitive function including: (i) Learning and memory, (ii) Visuospatial and motor function, (iii) Attention-concentration, (iv) Language, (v) Social cognition and emotions, and (vi) Executive functions. Each cognitive domain is broken into numerous subdomains [13]. In every cognitive domain several cognitive functions, which determine complex capabilities and personal intellectual skills, are being involved determining the individual cognitive status (**Figure 1**) [14,15].

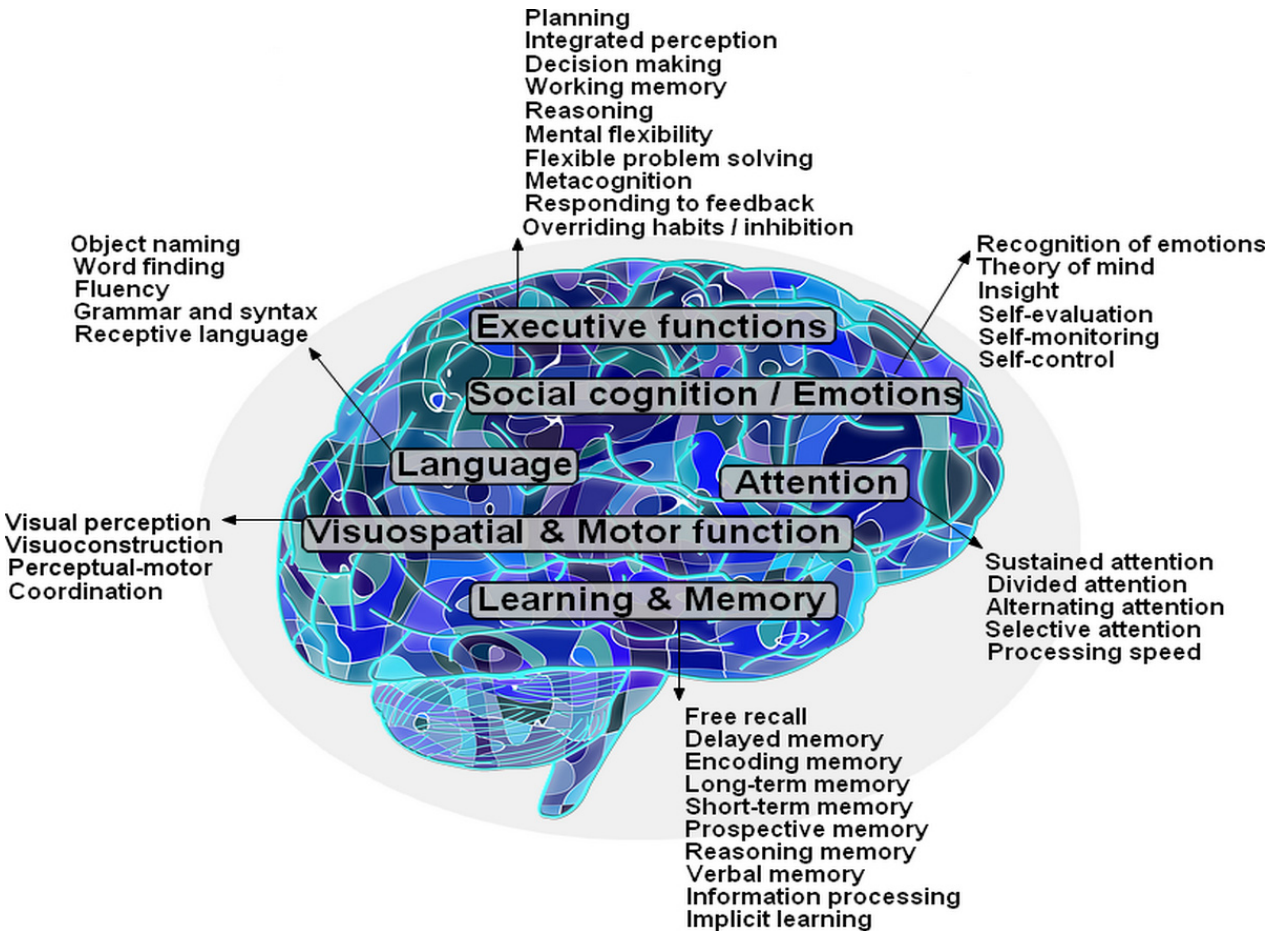

Figure 1: Major domains of cognitive function. Reproduced with permission of the European Respiratory Society ©. BREATH March 2017, 13 (1) e1-e9.

3. Cognitive Assessment

Cognitive function refers to the general competence of mental processes and it can be evaluated by the use of several clinical tools. Health professionals using available screening tools for mental function can screen patients for evidences of cognitive impairment. A wide range of tools has been developed for screening cognitive impairment in COPD and other pathological conditions while the duration of this procedure can last from few minute until several hours in the case of a formal neuropsychological assessment. The duration of cognitive tests designed for prompt cognitive evaluation takes from 4 to 12 minutes to be completed and gives a very important overview of patient`s mental status which can be taken into account from health professionals in respiratory settings in order to refer patients with very low scores to dementia-specialists (i.e. mental clinic) [15,16].

Popular and widely-used cognitive assessment tests are the following: A. Mini Mental State Examination (MMSE) [17]; B.Addenbrooke's Cognitive Examination (ACE) [18,19]; C. Montreal Cognitive Assessment (MoCA) [20]; D. Clock Drawing Test (CDT) [21]; and the Mini-Cog [22]. In cases that in-person cognitive screening is not possible; telephone interviews using telephone versions of cognitive tools such as the Telephone-MMSE or the "Telephone Interview for Cognitive Status (TICS)" can cover the need for cognitive assessment on distance [23]. These comprehensive cognitive tests found to have high accuracies in differenti-

ating mild cognitive impairment from normal controls [24]. After the implementation of one or a combination of cognitive assessment test, COPD patients with very low scores in those test, as inferred from the relationship of the patient's score to reference norms, can be considered as cognitively impaired and this should be taken into account when developing therapeutic strategies. Subsequently, a further cognitive evaluation is required using a comprehensive and multidimensional neuropsychological assessment in patients with borderline or worse cognitive scores [16] Health professionals who deal with older people and especially with elderly COPD patients could be advised to know how to administer at least one cognitive test when cognitive impairment of patients is suspected [15,25].

4. Mild Cognitive Impairment (MCI)

The primary stage of cognitive impairment is called mild cognitive impairment (MCI) and it is an official term used for first time by Reisberg and colleagues [26] to describe patients rated as a 3 on the Global Deterioration Scale (GDS) [26]. Specifically, MCI is defined as the "symptomatic pre-dementia stage" on the continuum of cognitive decline, characterized by objective impairment in cognition which, however, does not interfere with the simple activities of daily life [27,28]. COPD patients with MCI could present symptoms such as confusion and/or memory loss that are happening more often compared to age-match individuals or getting worse during the past 12 months [29]. However, those patients are not demented and thus the term MCI is used to describe a state in which cognitive decline is greater than normal age-related changes but not severe enough to meet the diagnostic criteria for dementia [30]. MCI is characterized by several common symptoms which are more severe or different compared those of normal ageing and have detrimental impact on all the aspects of COPD patients` daily life (**Table 1**) [31].

Table 1: Symptoms of MCI and typical ageing on cognitive status.

Typical ageing	Signs of Mild Cognitive Impairment (MCI)
Memory loss but ability to provide excuse of forgetfulness	Memory loss butinability to recall specific instances
Occasionally searches for words	Frequent searches for words, substitutions
Pauses to remember directions but preserved ability not to get lost in familiar place	Excessive time to return home while getting lost in familiar places is possible
Important event are still in memory; conversations are not impaired	Notable decline in memory for recent events and ability to converse
Interpersonal social skills are at the same level as they have always been	Loss of interest in social activities; Socially inappropriate behavior is possible

Patients with MCI are classified into the amnestic MCI (a-MCI), which is the most common form of MCI, or non-amnestic MCI (na-MCI) subtypes depending on whether their memory is substantially impaired. In case that a patient has an abnormally low performance in memory test that cannot be explained by person`s age and education, then a diagnosis of

a-MCI is made [32]. COPD patients without significant memory decline but with impairment in other cognitive domains such as language,visuospatial (not due to poor eyesight) and motor function, attention/concentration, and/or social cognition and emotions can be diagnosed with na-MCI [33]. Additionally, these subtypes of MCI can be further classified into single or multiple domains MCI according to the involvement of a single (i.e. isolated memory impairment) or more domains in patients with COPD [32,33]. Indeed, COPD patients with MCI can present deterioration in cognitive functioning of single or multiple cognitive domains including low capability in information processing, poor attention and concentration, weak memory, low executive functioning and self-regulation [34]. Further more, MCI can be relatively static (e.g., because of an injury, most commonly vascular) or progressive [35].

5. Prevalence of MCI in COPD

Several studies have found that the prevalence of cognitive impairment is increased in patients with COPD compared to general population [9,36]. The prevalence estimate of cognitive impairment vary amongst the studies in literature ranging from 12 to 88% as a result of different methodology and diagnostic criteria, and the diversity of the studied COPD populations [37]. Beginning from the age of 1982, Grant and colleagues showed that 42% of the COPD patients present evidence of moderate to severe cognitive impairment in comparison with only 14% in controls [38]. More recently a well conducted cross-sectional analysis from Villeneuve and colleagues recruiting COPD patients and healthy subjects reported that the prevalence of MCI was 36% and 12%, respectively [9]. Similar findings were also reported from another study demonstrating that MCI was present to 32.8% of COPD patients where as a 10.4% of the general population had evidence of MCI [36]. A meta-analysis of 2017 demonstrated that the prevalence of MCI is ranging from 23% to 42% in COPD while one out of four COPD patients will present evidences of MCI [39]. Additionally, COPD patients have approximately doublerisk of developing MCI than controls [10] and the riskis also increasing by longer COPD-duration [40]. Indeed, the risk for MCI increased from 1.60 (95%CI: 0.97-2.57) in patients having COPD of 5 years or less to 2.10 (95%CI: 1.38-3.14) in patients suffering longer than 5 years from COPD [40].

6. Lung Function and Cognition in COPD

The relationship between lung function and cognition has been investigated in numerous studies, which recruited large populations of healthy individuals [41-47] and COPD patients [5,48-51]. Those findings suggest that the status of cognitive function can be associated with lung function impairment. The relationship between impaired lung function and cognitive impairment is also reflected to the higher prevalence of cognitive impairment in COPD. About two decades ago, the comprehensive study of Chyou and colleagues [41] recruiting 3036 healthy individuals with a 3-year follow-up, demonstrated that force expiratory volume

at 1 second (FEV1) during middle age was a significant predictor of cognitive capacity in the later life after taking into account the contribution of age, level of education, stroke, sedentary job activity, non-manual occupation, height, generation,and speaking ability [41]. More recent, Richards and colleagues [46] investigated the lung function and cognitive ability in a longitudinal birth cohort study including 1778 individuals. This study reported that cognitive function and FEV1 are positively associated across the life course suggesting as possible explanation the parallel action of endocrine, autonomic, and motor control systems on respiration and higher mental function [46]. Similarly, Sachdev and colleagues [51] reported that decreased lung function is related to poorer cognitive function and increased subcortical atrophy in mid-adult life [51].

7. Pathophysiological Mechanisms and Risk Factors of Cognitive Impairment in COPD

The pathophysiological COPD-related mechanisms contributing to cognitive decline and the impact of risk factors on the development of cognitive impairment are not yet clearly understood. There is a general concept proposed for cognitive impairment in COPD, suggesting that increased inflammation and oxidative stress, as well as the lack of physical activity, may express the ageing process and result in increased age-related neurodegenerative changes [52]. Indeed, increasing age and low level of education are associated with cognitive impairment [53,54]. Additionally, several other risk factors for cognitive deterioration in COPD demonstrate both independent and overlapping contribution towards the development of cognitive impairment and have been reported in the literature [15]. The plethora of those factors which are often overlapping demonstrates that cognitive impairment in COPD cannot be explained only by single factors indicating that the development of cognitive deficits is a complex and multifactorial issue (**Figure 2**).

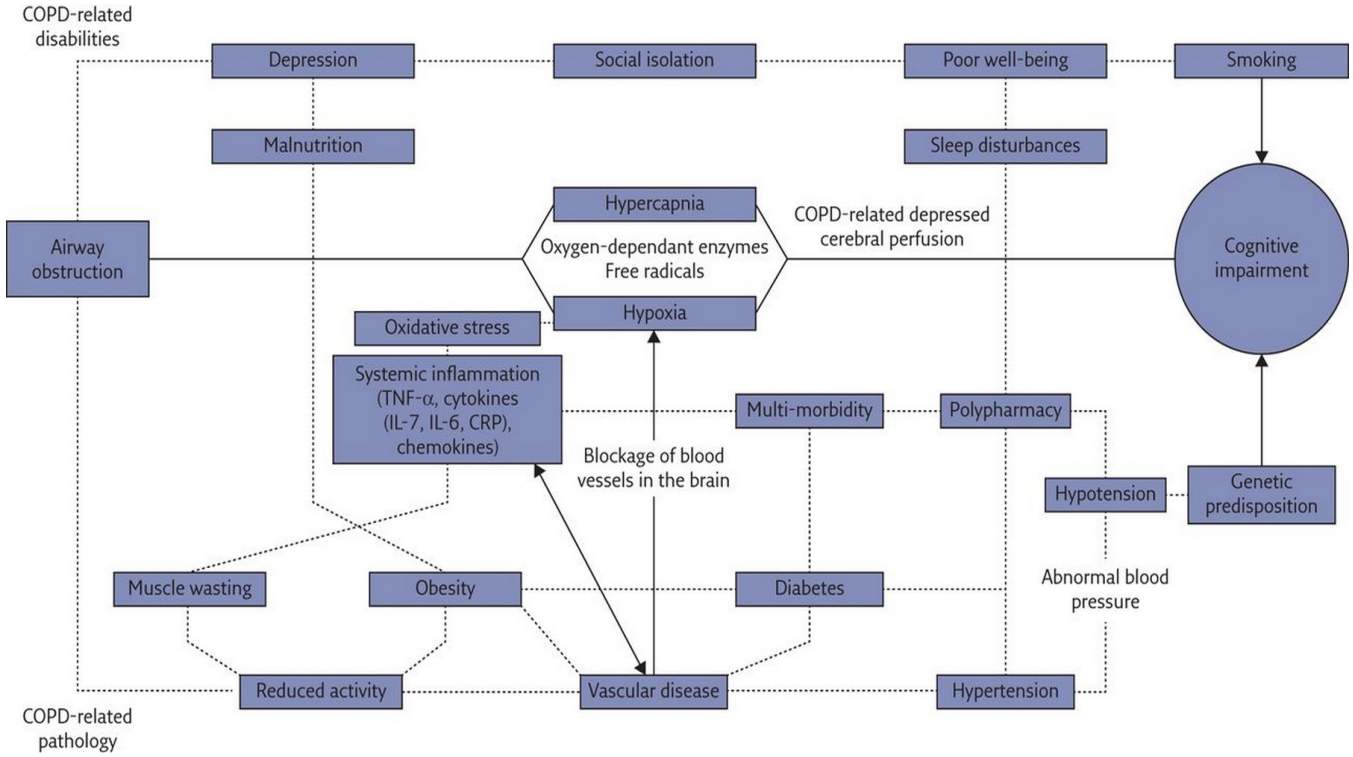

Figure 2: Determinants of cognitive impairment with potential independent and overlapping impact on cognitive function in COPD. TNF-α: tumour necrosis factor-α; IL-1: interleukin-1; IL-6: interleukin-6; CRP: C-reactive protein. Reproduced with permission of the European Respiratory Society ©. BREATH March 2017, 13 (1) e1-e9.

The reason that incidents of cognitive impairment in COPD are more frequent compared to general population, is hiding behind the COPD pathophysiology when other factors such as stress/depression, smoking, polypharmacy, and genetic predisposition, are excluded [55-58]. More specific, the patholophysiological mechanisms as well as the independent impact of risk factors on cognitive function that may contribute to the development of cognitive impairment in COPD include the followings:

7.1. Accelerated ageing and age-related changes

Patients with COPD experience an accelerated ageing [59-61] which indicates that age-related changes associated with the genesis of cognitive impairment may be occurred earlier in those patients. Briefly, ageing has the greatest negative impact on the hippocampus which is a region of the brain involved in the formation and retrieval of memories [62]. Hippocampal atrophy was evident on magnetic resonance imaging, with significantly smaller right and left hippocampal volumes in patients with COPD across the spectrum of disease severity [63]. Moreover, cerebral arterial narrowing/stiffness usually occurred after the age of 65 years old may decrease blood flow to the brain, which can further impair memory and lead to changes in cognitive skills [35]. Furthermore, the accumulation of amyloid-beta plaques and tau (amyloid pathology) that are linked to brain atrophy and neuronal dysfunction in brain interfere with neuronal synapses [64]. Also, an age-related decline in hormones and proteins that protect and repair brain cells and stimulate neural growth has been observed [65,66].

7.2. Hypoxia

COPD is marked by low oxygen levels that can lead to a chronic or acute hypoxic condition and cause neuronal damage [67]. Low oxygen availability is an independent risk factor for cognitive impairment because brain, which has almost the highest oxygen demand compared to other organs in human body (biggest oxygen consumers; liver: 20.4%, brain: 18.4%, and heart: 11.6%) [68], is highly sensitive and exposed to ischemic damage. Additionally, hypoxemia in COPD seems to play a crucial factor for the development of cognitive impairment as it affects the oxygen-dependent enzymes that are important in the synthesis of neurotransmitters such as acetylcholine [69]. Moreover, mild to moderate hypoxia has also been found to impair neuronal protein synthesis and synaptic plasticity [70]. Patients with COPD, even those who are not hypoxemic at rest, frequently experience a significant fall of oxygen saturation during exercise that is attributed to the imbalance between oxygen delivery and demand at exertion [71]. Indeed, exercise-induced oxygen desaturation (EID) due to insufficient oxygen supply to meet the metabolic demand of the brain can accelerate the loss of cerebral neurons over

the time [72]. Nevertheless, Liesker and colleagues [73] have reported that both hypoxemic and non-hypoxemic COPD patients have a worse cognitive status in general compared to age-matched healthy subjects [73]. Furthermore, cognitive performance of oxygen dependent patients has found to be worse than non-oxygen dependent COPD patients and an age-matched control group based on cognitive tests measuring cognitive functioning and mood status [74].

7.3. Hypercapnia

Another pathophysiological characteristic in COPD is the increased levels of carbon dioxide partial pressure (PCO_2) that are observed in some patients at rest or at exertion. Respiratory mechanics impairments, reduced ventilation (hypoventilation), hyperinflation, and reduced gas exchange capabilities (ventilation/perfusion mismatch) in COPD may account for carbon-dioxide retention in some patients, which may lead to hypercapnia [75-78]. Lower cognitive performance has been found to be related with higher PCO_2 levels and the occurrence of resting- or exercise-induced hypercapnia [48,79-81]. Klein and colleague [80] also reported that elevated PCO_2 levels are related to lower reaction time, delayed memory, slower information speed processing, and deficits in attention and concentration in patients with COPD [80]. Özge and colleagues [81] showed a correlation between hypercapnia and cognitive impairments, functional impairments and the frequency of sleep disturbances in patients with COPD [81]. Furthermore, the combination of chronic hypoxia and chronic hypercapnia has been shown to have detrimental effect on cognitive performance in COPD [82].

7.4. Prolonged inflammation

Reduced lung function is associated to increased levels of systemic inflammatory markers (i.e. CRP, TNF-a, IL-1B, IL-6) promoting degenerative processes and neurovascular damage, when are persistently elevated, and thus increase the risk for cognitive impairment in COPD patients [83,84]. Brain tissue may be damaged by either acute or chronic inflammation processes as both can induce the release of neurotoxic products such as reactive oxygen species and certain enzymesin harmful levels for the brain tissue [85]. Indeed, the prolonged inflammation as a systemic effect of patients with COPD, is linked to accelerated aortic atherosclerosis [86], neurodegeneration [87], and poor neurogenesis [88]. Substantial increased levels of inflammation in the brain can have deleterious consequences for neuronal, cerebrovascular, and cognitive function [89].

7.5. Vascular dysfunction and coexisting comorbidities

Several comorbid conditions may arise in COPD as a consequence of common risk factors, primarily tobacco smoke, systemic pro-inflammatory state, and sedentary lifestyle. [90,91]. Noticeably, a 25% of COPD patients older than 65 years suffer by two chronic conditions and this figure rises to 40% in population over 75 years old [92]. A prevalence of 21%

of previously unknown heart failure has been reported in COPD patients [93] while there is a recognized co-occurrence of heart failure and cognitive problems [94]. Indeed, incidents of heart failure may be related with the higher prevalence of cognitive impairment in COPD [95]. Moreover, endothelial dysfunction which starts early in the course of COPD and is related to the heart failure [96] as well as the occurrence of increased arterial stiffness [97,98] probably represent the onset of atherosclerotic disease [99]. Evidence has shown a relationship between endothelial dysfunction and MCI [100] likely because endothelial dysfunction is a step towards to atherosclerosis [101] that may have a negative impact on carotid arteries which are the main suppliers of blood to the brain. Moreover, vascular disturbances resulting in systemic hypertension or increased intracranial pressure are a risk factor for ischemic cortical infarcts and cognitive impairment [102,103]. In contrast, systemic hypotension related to cerebral hypoperfusion in response to reduced blood flow, may cause protein synthesis abnormalities and be also attributed to reduced oxygen availability. This can result in neurodegenerative lesions contributing to the development of cognitive impairment [104]. Furthermore, disturbances in glucose metabolism that are more frequent in COPD patients, increase the risk for diabetes mellitus (RR 1.8, 95%CI 1.1-2.8) [105,106] which is associated with moderate decrement in cognitive functioning [107]. Also, obstructive sleep apnoeacan be added to the panel of the most frequent comorbidities in COPD [108] which can also decrease cognitive performance. [109].

7.6. Other COPD-related risk factors

Mood disorders such as anxiety and depression are common in COPD patients and may be mediated by cognitive processes [110-112]. It is fact that functional limitations of COPD patient and reduced quality of life can cause or exacerbate stress and depression [113]. Around 40% of COPD patients are affected by depressive symptoms while a similar portion also experience moderate to high levels of anxiety [114-116]. A meta-analysis [117] demonstrated specific cognitive deficits that were found in patients with COPD and high levels of depression. Impairment in memory, executive functions and processing speed of information was related to the severity of depression [117].

Moreover, tobacco smoking, which appears to modulate brain function through nicotine, has negative effects on cognitive function [118,119]. Tobacco smoking is also associated with a general sedentary lifestyle and lack of exercise that can contribute to cognitive decline in COPD [120,121]. In contrast, an increase in physical activity and exercise within the frames of Pulmonary Rehabilitation [122-124], and intellectual activity [125,126] seems to have significant beneficial effects on cognitive function.

Poor quality of sleep especially when it is accompanied by obstructive sleep apnoea syndrome may also be accountable for cognitive impairment in COPD [127,128]. Findings

have shown that higher levels of fragmented sleep and lower sleep efficiency are associated with a 40% to 50% higher risk of a significant decline in executive function in older community-dwelling men [129]. More studies, however,to assess quality of sleep and cognitive status in COPD, are needed.

Last but equally important, genetic and environmental factors which can influence the development of brain and cognitive functioning [58], may determine the susceptibility of COPD patients towards to cognitive impairment. Moreover, impaired cerebral synthesis capacity of neuro transmitters such as dopamine is associated have an impact on cognitive function [130].Future studies on determinants and reliable risk factors of cognitive impairment in COPD, are needed.

8. Consequences of Cognitive Impairment in COPD

Consequences of cognitive impairment in COPD are individual and may significantly differ amongst patients [131]. There are cognitive areas which are more vulnerable to deterioration compared to others [132] demonstrating several detrimental effects on numerous aspects of patients functioning and health status [37,80,133]. Cognitive impairment may cause difficulties with performing daily activities, especially those that involve memory or complex reasoning [133,134]. It is also associated with certain limitations in intellectual functioning and adaptive skills including conceptual, social, and practical skills [135]. Incalzi and colleagues demonstrated an association between low results on cognitive tests and disability in activities of daily life in patients with COPD [136]. Limitations on daily life due to cognitive deficits cause an immediate discomfort in COPD patients, increase stress and depression, and affect quality of life [137].

Moreover, cognitive impairment, especially memory problems and poor executive function, may interfere with patients' ability to adhere to their medication regimen and to perform other aspects of COPD-related self-management [138]. Patients may lose motivation (i.e. proactivity and compliance) in case that they forget given guidelines, requests or instructions, and, consequently, present lack of adherence overshadowing therapeutic outcomes [139]. Besides that, COPD patients with poor executive functioning may display a discrepancy between "theory and praxis" as they are able to report specific instructions as given by health professionals but they cannot translate these into specific behavioral and motor plans and activity [140]. For instance, an improper use of (inhalation) medication and difficulties in handling guidelines in daily life are usually observed [141]. As result, a loss of patient`s independence and decrease in treatment compliance can be occurred impeding the course of respiratory treatment [142]. The poor compliance also increases the risk of acute exacerbation in patients with COPD. [143].

Furthermore, increased rates of respiratory-related and all-cause hospitalization and

mortality have been reported in patients with coexisting COPD and cognitive impairment. [144]. Additionally, a significant correlation has been shown between the length of hospitalization (number of days in hospital) and the quality of life in COPD patients with worse cognitive performance [145]. A possible explanation for the worse prognosis of COPD patients with cognitive impairment is that those patients have likely a poorer self-management and generally worse health status and, therefore, present worse therapeutic outcomes [146].

9. Treatment of Cognitive Impairment within the Frames of Pulmonary Rehabilitation

Early detection of cognitive deficits is crucial to allow interventions aimed at controlling the progress of cognitive impairment and prevent any negative consequences in the course of respiratory treatment in COPD [15]. Despite the fact that only some patients regain cognitive function, cognitive impairment should be considered as a condition with a high potential of reversibility as there are some modifiable factors that can be corrected and thus improve cognitive status in patients with COPD. According to the literature factors including levels of physical activity [147,148] and exercise [149,150], balanced diet [151], cognitive training [152], and the social engagement [153] can be modified in a way to become strong promoter of cognitive health in patients with COPD.

Pulmonary rehabilitation (PR) is known as a multidimensional program of exercise and education that can be highly recommended within the frames of therapeutic plans in patients with COPD [154]. Besides pharmacological intervention, patient enrolled in a PR program have the opportunity to improve modifiable factors with favorable effects on cognitive function. Exercise training, which is the cornerstone of pulmonary rehabilitation [155], is the best available mean of improving exercise capacity and activities of daily living in COPD [155, 156], therefore, it may both prevent and improve cognitive deficits in COPD. Indeed, regular physical activity and exercise have a protective role against cardiovascular disease, and this likely extends to the risk of cognitive impairment in COPD [157]. Furthermore, exercise seems that cause an increase of the number of neurons in hippocampus [158] and increase cerebral neural activation [159] mediating cognitive function. Evidence has shown that COPD patients who adhere to exercise routinely over 1-year maintain executive function [160]. Pereira and colleagues [161] investigated the effects of a 3-month PR program in patients with COPD on cognitive function and reported significant improvements in cognitive performance [161]. Moreover, short-term PR programs of 3-week duration seem to have clinical improvements in visual attention, verbal memory and visuospatial skills in cognitively impaired COPD patients [162]. Emery and colleagues [163] demonstrated that acute exercise is associated with improved performance on the verbal processing, suggesting that acute exercise may benefit aspects of cognitive performance among patients with COPD [163]. Given the fact that PR programs also emphasize behavior change through collaborative self-management, translation of increased exercise capacity to greater participation in activities involving physical activity

may be possible [164,165] with favorable effect in cognitive status of patients with COPD.

Besides the benefits of exercise, nutritional support in PR may be also beneficial regarding cognitive function in COPD [151]. The relationship between poor nutritional status and cognitive decline was first described by Goodwin and colleagues [166], who demonstrated that individuals with low levels of vitamins C and B_{12} have worse memory performance on the Wechsler Memory Test [166]. More recent, low concentrations of vitamin D found to increase the risk of cognitive decline [167]. A balanced diet that provides patients with all the essential vitamins and minerals, has been recommended as effective strategy to counteract neurological and cognitive disorders [168]. Additionally, intake of dietary components such as n-3 and n-6 fatty acids seems to be helpful as they may ameliorate cognitive function by lessening the impact on amyloid deposition within the brain [169-171].

Cognitive training or intellectual stimulation, and socialization within the frame of PR program could also benefit COPD patients with cognitive impairment. Randomized control trials employing intellectual training reported that cognitive interventions can produce protective and potentially long lasting benefits in several cognitive domains [172]. The concept of intellectual stimulation as a beneficial factor in cognitive impairment in COPD can be based on the "cognitive reserve" theory suggesting that individual differences shaped by inherent characteristics and external sources including intelligence, education, occupation, and intellectual activities, can increase neurogenesis creating an abundance of neuron synapses and thus preventing cognitive impairment [173-176]. Similarly, social engagement may boost neurogenesis [153] and can also improve self-esteem [177], reduce stress and depression [178,179] and, therefore, it may carry an important protective effect against cognitive decline in COPD. In addition, the administration of oxygen may also lead to cognitive enhancement improving brain function in patients with COPD [180].

10. Conclusion

Cognitive impairment is a frequent limitation in COPD patients and deserves a particular attention because of its detrimental consequences on many aspects of patients functioning and health status. It may also affect the course of respiratory treatment and, therefore, cognitive evaluation should be part of respiratory assessment, especially in patients suspected for cognitive deficits [15]. COPD pathology seems to be accountable for the high prevalence of cognitive impairment in COPD patients while hypoxia and systemic effects are common risk factor for the development of cognitive deficits. Pulmonary rehabilitation as comprehensive therapeutic intervention can provide opportunities to attenuate cognitive decline in COPD.

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