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Neurocognitive Impairment as Systemic Effects of COPD

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Abstract

Mild cognitive impairment (MCI), also known as incipient dementia, is characterized by the decline of cognitive function greater than expected for a certain age and educational level of the individual but not severe enough to interfere with their daily activities. However, this mild cognitive impairment affects several areas: visuospatial, memory, attention and fluency and it is a significant concern because it decreases the quality of life and treatment adherence of these patients. On the other hand, evidence suggests that individuals with Chronic obstructive pulmonary disease (COPD) also present an important risk of falls: 46% of these patients experience a fall/year, sometimes with fatal consequences. Standard clinical balance measures can predict the risk of falls in this population. Moreover, increased inflammatory biomarkers are associated with the decrease of cognitive functions and a higher risk of falls in this population. Patients with COPD have a higher balance and cognitive impairment than their healthy peers. Therefore, it is important to identify, assess and understand the relevance of these comorbidities in order to characterize the full clinical spectrum of COPD and adjust prevention strategies, given the devastating consequences of these problems.

Keywords: balance, falls, dementia, cognition, COPD

1. Introduction

COPD is recognized as a disease with many systemic components [1]. Among them, the neuro-psychical component (anxiety/depression), has already been recognized. Besides this, in the last decade, research has been initiated on the neuromorphological substrate to explain whether certain manifestations such as cognition alteration, the occurrence of balance disorders, etc. could also be due to the impact of COPD, or would only be manifestations

related to age and/or other comorbidities. This paper presents an overview of the state of knowledge in this last field.

1.1. Summary

- Cognition – domain and modulating factors.
- Balance disorders: nosology, prevalence, clinical consequences.
- COPD: fundamental pathophysiological mechanisms susceptible to alter cerebral function.
- Clinical consequences of affected cognition; measure methods.
- Therapeutic implications; preventive strategies.

2. Cognition: domain and modulating factors

There are multiple classifications of cognition, of which that proposed by Dal Negro seems the most appropriate for the purpose of this chapter. According to that, its domains and subdomains are: (a) executional function with the subdomains: attention, problem solving, planning and reasoning; (b) language, with the subdomains: comprehension and verbal fluency; (c) memory, with the subdomains: memory-based tagging and work memory; (d) praxis, with the subdomains: motor-ideative, ideative and visual constructive [2].

The distinction between any cognitive impairment and mild cognitive impairment (MCI) should be clarified. The latter refers to a brain function syndrome involving the onset and evolution of cognitive impairments other than those age and education related, but that are not significant enough to interfere with daily activities [3]. To date (2017), one of the most comprehensive meta-analyses that have specifically investigated prevalence MCI in the context of COPD, included 23,116 people with COPD, and showed MCI prevalence of 25%, raising up to 32% if any cognitive impairment is assessed [4].

Compared to the prevalence of MCI in the general population, which is in the range of 10–20% in older adults, a rate of 25–32% present in patients with COPD is more than worrying [5].

But equally important is the relationship between the various cognitive domains affected in COPD patients and the disease itself. This is because the prevalence of impairment varies among the different cognitive domains. What is more, the psychometric profile impairment would be associated with the variable components of COPD such as hypoxemia, hypercapnia, lung function, exacerbations or disease severity.

Although one cannot speak about a specific profile encountered in “pure” COPD, that is, the one without comorbidities, the most frequently affected subdomains are attention, naming, visuospatial, memory, motor and executive function and mood decrements (fear and antinociception) [6–10].

We must be aware that COPD severity (hypoxemia/hypercapnia, pulmonary obstruction and exacerbations), factors typically present (age and smoking) as well as various combinations (comorbidities, education level, physical activity, nutritional status, etc.) make up in a complex mosaic. Assigning cognition alterations to the underlying disease (COPD), implies for this reason, an extremely laborious and unlikely effort to distinguish among these factors. An example, in a prospective study of 62 patients with COPD, it was possible to see how cognitive impairment varied depending on the stage of the disease: exacerbation, at discharge or when the stable phase was reached; unlike other studies, this research followed the same patient at all 3 different stages of his disease. Cognitive assessment was measured by Montreal cognitive assessment (MoCA) test. From exacerbation to stable COPD, all the clinical variables improved step-by-step: visual-constructional, attention, language, abstraction, delayed recall and orientation (from exacerbation to discharge), visual-constructional and naming (from discharge to stable phase) and taken as a whole, from exacerbation to stable COPD: naming, attention, language, abstraction and delayed recall [11].

Thus, differences in studies such as (a) various study designs and methodological limitations: lack of clinical assessment of airflow impairment, severity of COPD, heterogeneity of assessment moment (stable phase, exacerbation and long-term oxygen therapy [LTOT]), small sample size, lack of appropriate referent group, diagnostic criteria for cognitive impairment (psychometric tools and neuroimaging), (b) the use of different definition, (c) lack confounder adjustment procedures: comorbidities, age, active smokers, level of education, etc., may explain the wide range of prevalence rates of cognitive impairment in COPD from 5.5% up to 77% [12, 13].

2.1. Balance disorders: nosology, prevalence, clinical consequences

Chronic illnesses in general as the disease progresses develop debilitating features, and COPD is no exception. Age and other features may include lower limb muscle weakness, overall fatigue, dizziness, different functional impairment, body imbalance and others [14].

Among them we will refer to balance impairment, which can lead to the loss of coordination and implicitly to falls.

Involuntary falls are incidents that can occur at any age, more frequently in the elderly, with possible devastating consequences. Individuals aged over 65 would experience at least one fall per year [15]. In a prospective study, the incidence of falls was more than four times higher in patients with COPD, than in healthy individuals with respect to gender and age [16].

Due to comorbidities, elderly patients are often polymedicated: anxiolytics/sedatives, anti-hypertensives, corticosteroids, etc., medications that can be responsible for balance disturbances. According to a research conducted by Roig, the use of corticosteroid therapy in COPD population has been estimated to be ~61.5% for inhaled and ~8.3% for oral corticosteroids [17]. Corticosteroid therapy interferes with the production of contractile proteins (increase intracellular proteolysis) resulting in muscle weakness conducting to falls. Thus, in order to

relate falls to COPD we must exclude other confounders: polypharmacy, decreased vision, impaired mobility (arthrosis) and multiple other comorbidities.

Two other factors, such as sedentary life style and systemic inflammation, should not be neglected either: the former is almost constantly encountered and the latter in about 30% of cases [18].

Severe COPD stages as well as exacerbations are accompanied by an increased risk of falls [19].

Dispnoea, muscle mass loss (especially in the thighs) and decreased exercise endurance will reduce the ability of COPD patients to perform daily activities and limit their exercise tolerance, creating a downward spiral that will lead to generalized immobility [20].

Difficulties in achieving day-to-day activities and related instrumental activities contribute to a reduced quality of life, but in the event of falls, devastating effects may arise on global function and even on life expectancy. Except for a major physical trauma event, the disorder is resulting in loss of functional independence and social interaction.

Several studies have shown that the history of falls in the previous year is predictive of relapse [21].

Repeated falls will lead to insecurity, fear and lack of confidence in performing daily domestic activities. In a recent study, that included 93 patients with COPD, 32% had a degree of body balance impairment during the performance of dynamic activities, compared to 5% in the control group ($p = .0005$) [22].

Fear and lack of confidence in performing everyday domestic activities will develop a chronic status of loss of movement autonomy which can lead to muscle deconditioning, higher global fatigue and greater loss of body balance. As a consequence, the adherence to treatment will decrease, especially to rehabilitation programs [19].

The most common used tests are: the Berg Balance Scale (BBS), Falls Efficacy Scale-International (FES-I), Timed Up and Go (TUG), single-leg stance test (SLS) and activities balance confidence (ABC).

Studies that tried to ascertain whether there is a correlation between COPD phenotypes and nutritional status have generated contradictory results. Some of them have found that the cachectic/emphysematous phenotype would be more prone to falls, considering that loss of skeletal muscle and weakness would be the main cause [23]. Others, by contrast, mention that the bronchitis/obese phenotype would have a higher risk of falls, due to the fact that the obese patients would record the intensity of fear more than the cachectic phenotype [24].

The overall conclusion is that patients with COPD have greater balance impairment than their healthy peers.

2.2. COPD: fundamental pathophysiological mechanisms susceptible to alter cerebral function

Cognitive impairment is multifactorial, but a history of cigarette smoking, aging and educational level are recognized as major determinants [25, 26]. The origin of the cerebral dysfunction

in patients with COPD is still unknown, assuming the interference of several pathological relays: hypoxemia, oxidative stress, systemic inflammation, smoking, comorbidities, vascular-mediated brain pathology, neurotransmitter metabolism in the central nervous system (CNS), a decrease in physical functioning, genetic and epigenetic factors.

Hypoxia. In 1919, Haldane had a deep insight: “partial anoxia means not an appreciable slowing of life, but progressive, and perhaps irreparable damage to human structure.” This “irreparable damage to human structure” can also include brain damage [27]. After half a century, Krop and colleagues observed the neuropsychological benefits of continuous oxygen therapy in COPD [28]. However, the first major randomized clinical trial (Nocturnal Oxygen Therapy Trials – NOTT), appeared in 1980, when the effects of continuous or nocturnal oxygen therapy on hypoxemic in COPD were investigated [29]. After the re-examination of the NOTT, it was possible to see that 42% of patients with COPD had moderate-to-severe cognitive impairment compared to 14% among controls [30]. In a follow-up of the NOTT cohort, it was observed that the neuropsychological deficit parallels the degree of hypoxia: 27% of those with mild hypoxemia to 62% in those with severe hypoxemia [31].

It is worthwhile discussing the mechanisms of response of the brain to hypoxemia. There is a very interesting mechanism for counteracting cerebral hypoxemia, the so-called cerebrovascular oxygen reactivity, which ensures blood flow up to 200% in the conditions of oxygen desaturation produced by chronic hypoxemia, nocturnal or exercise induced. For this reason, cerebral blood flow is much higher in hypoxemic than in non-hypoxemic COPD patients and even healthy controls [32, 33]. The same mechanism also explains that during rapid eye movement (REM) sleep, which accounts for about 13% of total sleep time in COPD patients, there is no cerebral hypoxemia. Surprisingly, during nonrapid eye movement (NREM) sleep, it is not known why, cerebrovascular oxygen reactivity is missing [34].

Nocturnal desaturation events are commonly met in 38–70% non-hypoxemic COPD patients [35]. Under these conditions, when the cerebrovascular oxygen reactivity mechanism is inoperative, the effect of night-time desaturation should injure the central nervous system (CNS). This was also the goal of a study of 115 non-hypoxemic COPD patients grades 2 and 3, without sleep apnoea, to which it was dosed a serum surrogate marker, namely S100B (a calcium binding protein produced in brain damage), and at the same time neuromuscular function via motor cortex activation and excitability and maximal voluntary quadriceps strength measurement was assessed. Absence of cerebrovascular reactivity would be the mechanism leading to brain injury formation during NREM sleep desaturations, which was found in approximately 50% of non-hypoxemic COPD patients [36].

The effort in daily activities would be likely to cause brain damage in severe COPD hypoxemic patients; emphasizing desaturations, inducing increase of frontal lobes choline (which is a reliable marker of myelin destruction with alteration of neuronal membrane turnover) corresponding to white matter hyperintensities on magnetic resonance imaging (MRI) [7].

In a study that enrolled younger patients (45–65 years) with COPD, low baseline oxygen saturation ($\leq 88\%$) was strongly related to cognitive impairment (adjusted OR = 5.45). But what is more relevant is that in the same study, regular use of supplemental oxygen therapy in home setting

decreased the risk for cognitive impairment (OR = 0.14; $P < 0.0001$) [37]. It is a recognized fact that long-term oxygen therapy (LTOT) is able to protect significantly ($p < 0.022$) the cognitive functions from COPD-induced deterioration. Another fact is that the patients with mild cognitive impairment COPD induced are unaware of the risk that involves repetitive desaturations to produce conversion from mild cognitive impairment to dementia, if nothing is done with LTOT [38, 39].

Therefore, continuous or even intermittent hypoxia (efforts, daily activities and sleep) may cause changes in brain perfusion, transient deficits in neurotransmitter metabolism in the central nervous system with changes in brain neurochemistry and structure [7, 36, 40–42].

Although hypoxia is *per se* a damaging factor, it mostly acts in an additive manner in the development of structural abnormalities in the brain [43].

Chronic systemic inflammation. Inflammation as a driving force to the central pathology of the disease, in very recent years has been subjected to doubts and contestations [44]. Even in the definition of COPD, GOLD 2017 no longer mentions the contribution of chronic inflammation to the pathophysiological process [1].

However, patients with COPD, particularly when the disease is severe and during exacerbations have evidence of systemic inflammation: increased circulating cytokine, chemokine, and acute-phase protein levels or abnormalities in circulating cells. These mediators are derived from inflammatory and structural cells in the lung and interact with each other in a complex manner. Similar mediators that are found in the lungs of patients with COPD might also be increased in the circulation, presumed reached here through translocation or “spill-over”; this chronic low-grade systemic inflammation could underlie and potentiate comorbidities (muscle wasting/cachexia, cardiovascular diseases, osteoporosis, etc.) including central nervous system impairment [45, 46]. The chronic inflammatory status may contribute to vessel wall changes (endothelial dysfunction, stiffening of arteries and arterioles and impaired vascular reactivity) and may also have neurotoxic effects: synaptic dysfunction and neural cell apoptosis [46–49].

The inflamed endothelium overexpresses surface adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), facilitating the adherence of white blood cells to damaged endothelial surfaces. Interleukin 6 (IL-6) can stimulate the release of acute-phase proteins by hepatocytes, including C-reactive protein (CRP), serum amyloid A, fibrinogen and procoagulant factors, which further promote or amplify the inflammatory process [50]. Moreover, CRP fosters the uptake of low-density lipoproteins (LDL) by macrophages, which contribute to the increased prevalence of arterial plaques containing a lipid core in patients with COPD [51]. Accelerated atherogenesis and impaired endothelial function, caused by a vascular inflammation status is assumed to lead to microvascular dysfunction and cerebral small vessel disease (microbleeds and lacunar infarcts) having as a consequence cognitive and functional impairment [52].

On the other hand, COPD is frequently associated with cardiovascular diseases, obesity or metabolic syndrome, the contribution of comorbidities into the systemic elevation of IL-6

levels is difficult to disentangle. Some authors described an inflammatory-prone COPD phenotype, patients with an increased risk of exacerbations (OR = 3.7) and simultaneously more severe cardiovascular and cerebral abnormalities [53, 54].

Acute exacerbations of COPD. These patients had significantly poorer cognitive function compared with control participants 3 months after discharge from hospital [55]. During a severe exacerbation, in the context of hypoxemia, paroxysmal inflammation (increased platelet activity and coagulation) and a pre-existing endothelial dysfunction, plaque rupture can occur and consequences will be coronary obstruction and stroke. However, other studies have shown that cognitive impairment during the exacerbation period recovers during periods of stability [56].

Smoking. Smoking has pleiotropic disastrous effects: promotes atherosclerosis (endothelial changes), direct effect of neurotoxicity (heavy metal, nicotine and constituents of smoke), exacerbates hypoxia brain due to chronically elevated carbon monoxide causing a left shift of the oxyhaemoglobin dissociation curve, deteriorates lung function, favors the development of comorbidities which have a negative effect on cognitive processes. Chronic smoking is also involved in the production of pathogenic changes (decrease in the gray matter density) in areas where Alzheimer's disease develops (inferior parietal lobule and precuneus). Moreover, its deleterious action can continue even after smoking cessation [57–59].

Comorbidities. It is a recognized fact that general morbidity and the burden of disease increases with both age and cumulative pathology, and COPD is no exception.

In a study of 52 stable non-hypoxic COPD patients, Ersel Dag et al., found that subjects with better functional capacity and lower comorbidity had better cognitive function; according to this study, the MoCA would be superior to Mini Mental Status Examination (MMSE) in detecting cognitive decline [60]. A higher Charlson Comorbidity Index and a reduced functional level have induced cognitive decline; this is also the conclusion of another similar study with 1 year follow-up of patients with COPD, which at baseline hospitalization lacked cognitive impairment [61]. Cleutjens et al. in a cross-sectional observational study on 90 stable COPD patients compared to 90 matched non-COPD controls, analyzed general cognitive impairment and domain-specific cognitive impairment using a complex battery of 6 psychometric tests, after correction for comorbidities using multivariate linear and logistic regression models. They found a prevalence rate of 56.7% for general cognitive impairment, which meant four times higher compared to matched non-COPD controls. The most prevalent affected domains were planning and cognitive flexibility, where abnormal planning was observed in 16.7% of patients without comorbidities but in none of the controls without comorbidities, and abnormal cognitive flexibility was observed in 44.4 and 11.6% of patients and controls without comorbidities, respectively [9].

Diseases accompanied by hypoxemia and vascular damage (coronary heart disease, cardiac failure, hypertension and stroke) have a proven risk of developing neural damage that is amplified if active smoking is also associated [4].

Another comorbidity present in over 20% of COPD cases is Obstructive Sleep Apnoea Syndrome (OSAS), a disease that underlies many common pathological pathways. Through recurrent hypoxia, moderate–severe forms of OSAS are able to affect cognitive performance, especially by focusing on attention, complex thinking, learning and memory [62, 63].

Depression and anxiety are among the most common comorbidities of COPD, reaching over 70% in oxygen-dependent cases, and much more important is that onset of depression was predictive of cognitive decline among COPD patients [64].

COPD was associated with baseline and incident disability which progresses over time and cognitive impairment was found to have an additive effect on this disability [64–66].

Therefore, cognitive comorbidities may contribute to a substantial burden of COPD-related morbidity, especially by impairing quality of life, reducing physical activity, reducing adherence to treatment and increasing the frequency of hospital admission.

Oxidative stress. An increase in the level of reactive oxygen species (oxygen ions, free radicals and peroxides) leads to oxidative stress, which would alter the neuronal signals that produce neuro-inflammation with neuro-degeneration and implicitly with cognitive impairment [67]. The most important triggers for the development of oxidative stress in patients with COPD are cigarette smoke and systemic inflammation.

Other possible mechanisms. In a highly laborious study in 55 patients with moderate-severe COPD in stable period were determined: (i) cognitive ability (through a battery of 6 psychometric tests), (ii) structural brain abnormalities using 3T MRI to seek signs of small vessels disease (white matter hyperintensities, lacunes, cerebral microbleeds and enlarged perivascular spaces) and (iii) hippocampal volume as an area involved in memory process. The 55 patients were divided into 2 subgroups, cognitively high (25 patients) and low-performing (30 patients), having comparable demographics, clinical characteristics and comorbidities. No structural changes were found between COPD patients with low or high cognitive performance, demonstrating that small vessels disease would not represent a pathological pathway [68]. On the contrary, other authors provided evidence of significant white and gray matter abnormalities associated with cognitive dysfunction in patients with COPD without arterial hypoxemia or hypercapnia. Given 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 [69, 70].

Mitochondria are the intracellular organelles that provide aerobic respiration and cellular energy. As a result, mitochondrial diseases have as expression and localization the most oxygen-consuming tissues: skeletal muscles, central nervous system and heart. Depending on the load of mutant mitochondrial genomes, neurological expression ranges from mild cognitive impairment to dementia, or epilepsy, stroke-like episodes, ataxia, etc. In COPD, there are approximately 20% of cachexia cases in which a mitochondrial component might be involved [71, 72].

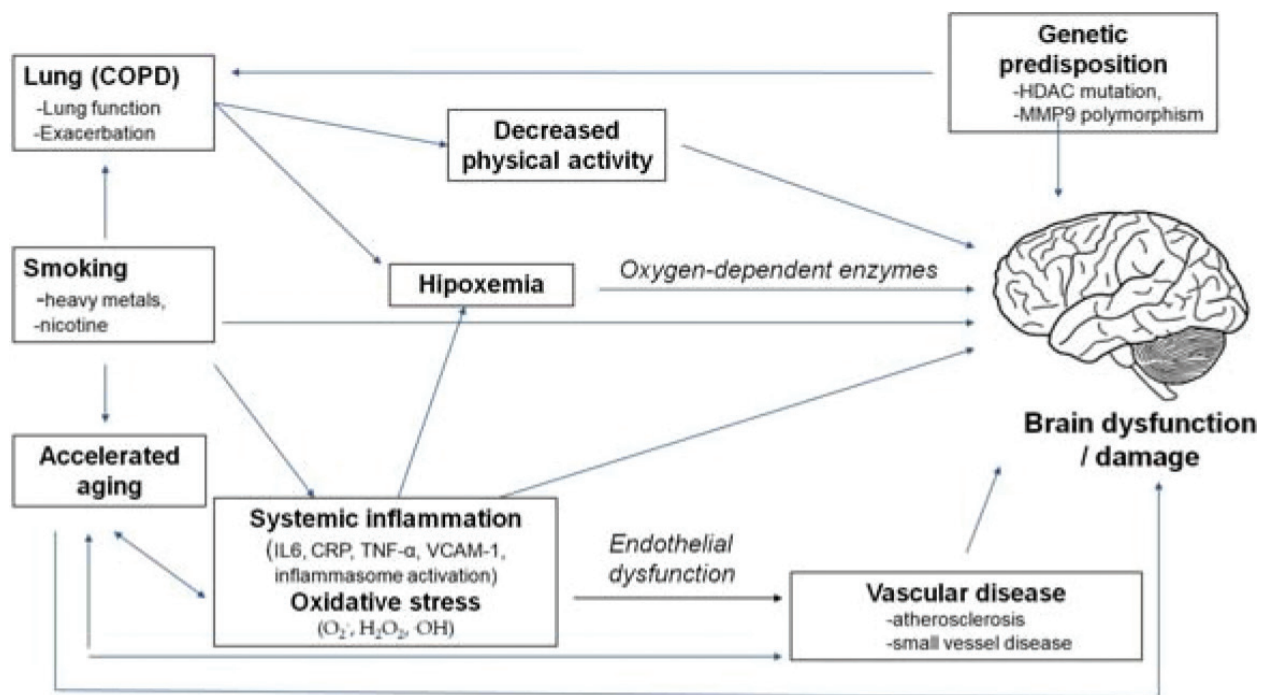


Figure 1. Potential mechanisms contributing to brain dysfunction and/or damage in elderly subjects with COPD. HDAC: histone deacetylase, MMP9: matrix metalloproteinase 9, IL-6: interleukin 6, CRP: C-reactive protein, TNF- α : tumor necrosis factor, VCAM-1: vascular cell adhesion molecule-1.

Many factors, generated by, or interconnected with COPD, could contribute to brain dysfunction and/or damage (Figure 1).

2.3. Clinical consequences of an affected cognition; measure methods

In order to diagnose MCI, besides the clinical and anamnestic examination, psychometric tests as well as neurochemistry and neuroimaging assessment are available.

Torres-Sánchez et al., in their meta-analysis listed more than 40 psychometric tests that were used [73]. The most used psychometric questionnaires are: the Mini Mental Status Examination (MMSE), the Clock Drawing test, the Trail Making test (TMT) A, the TMT B, Memory Impairment Screen (MIS); Montreal Cognitive Assessment test (MoCA) [74]. It is advisable to use a battery of tests, not a single one, to improve the result accuracy [75, 76].

Neuroimaging studies showed there are significantly lowered gray matter volumes in several brain regions as hippocamp [7], limbic and paralimbic structures [77], precuneus, bilateral calcarine, right superior temporal gyrus/middle temporal gyrus, bilateral fusiform, right inferior parietal lobule [78], cingulate and amygdala [8], dorsolateral prefrontal cortex [77] etc., evidenced by different neuroimaging techniques based on magnetic resonance imaging (MRI). Performance accuracy has increased by introducing voxel-based morphometry analysis also based on MRI. Using this technique, it was possible to show for the first

time gray matter volume alterations in stable COPD patients, even to those with subclinical cognitive impairment [79].

Passing over the slight contradictions or discrepancies between the results offered by these and other neuroimaging studies, what is common is heterogeneity and broad distribution of the lesions. Another important finding of neuroimaging studies is inferior parietal lobule and precuneus that are two regions altered also in COPD and Alzheimer disease.

Chronic airway involvement can be perceived as a strong aging factor leading to an early deterioration of cognition with a 10–15 years advanced age [2]. In a study on 301 stable moderate-severe COPD patients conducted by Schure et al. showed that cognitive functioning (especially, psychomotor speed and executive control) present in approximately 30% of cases would be associated with greater disease severity and poorer physical functioning (as measured by the six-minute walk test, total steps per day and grip strength). And these results are more relevant as patients were “healthier” COPD, namely the patients without comorbidities known underlying inflammation (Charlson Index = 0.9–1.2) [80].

Due to the non-homogeneous distribution on the brain mapping, patients will experience various and multiple disorders, most of which are reflected by difficulties in naming, memory, visuospatial, executive function and mood decrements.

COPD-related dyspnoea is a strong driver to anxiety, panic or/and depression and reduced quality of life. But, development of a secondary cognitive impairment component may contribute to increased behavioral disturbances; these may distress much more the family caregivers which need to cope with behavioral changes.

In a study on 88 patients with COPD, Turan et al. showed a positive correlation between declining of cognitive function, assessed by MMSE questionnaire, and suboptimal inhalation adherence, increasing hospitalizations and emergency visits [81]. In another study of 265 patients with COPD, adherence was measured using a tool incorporating sophisticated electronic devices to mark time and correctness of the technique; adherence over the study was 22.9% of what would be expected if all the doses had been taken correctly and on time, but more important adherence was negatively influenced by impairment in cognitive function [82].

According to statistics, 41% of patients with stable COPD who undergo rehabilitation would suffer from any cognitive impairment. Inclusion and completion of a pulmonary rehabilitation program is however affected by the presence of cognitive impairment, the drop-out number being higher in those with cognitive impairment. However, the comparison of the different parameters (functional status, health status and psychological well-being) to the patients able to complete the program does not differ between cognitive impairment patients and those with no cognitive impairment, this being an argument that patients suffering from cognitive impairment can benefit from the programs rehabilitation [83]. Do not forget to investigate factors related to balance changes in patients with COPD. Although the risk of falls may seem less important than the consequences of COPD itself, falls are associated with increased mortality, reduced independence, poorer quality of life and lower level of physical activity.

Depression and anxiety are found in high proportions (30–70%) and identifying the coping styles in patients with COPD represent an important aspect of the individualized treatment of the patient, because the coping style can be both adaptive, implying the stress reduction and maladaptive, situation in which the maintenance and the amplification of the current symptomatology are present or can determine the appearance of some new symptomatic elements and behaviors [84].

The fact that cognitive impairment would occur at younger age [2], would cross a subclinical period [79] and would present at least 30% of cases [80], all of which signals us that cognitive impairment may be an early indicator of emerging risk of frailty and poor overall mental functioning among COPD patients.

Cognitive impairment has also been reported to worsen over time due to both the aggravation of COPD and the increase in burden represented by the progression and/or complications of comorbidities [85]. Chang et al. reported that the co-occurrence of COPD and cognitive impairment in a 3-year prospective study was associated with increased rate of disability, hospital admission and mortality [86].

3. Therapeutic implications; preventive strategies

How to deal with a COPD patient who might be suffering from cognitive impairment? Based on growing evidence in recent years, it is reasonable that cognitive assessment in subjects suffering from chronic obstructive disease should enter the routine of diagnostic procedures to grade the overall impact of patients' respiratory condition. Multiple areas of cognition being altered in varying degrees, may explain a poor awareness of the disease and may compromise the individual's ability to manage his or her own care and adherence to treatment. The clinician, who observes signs of forgetfulness, disorientation or balance trouble and/or even poor adherence to medical treatment, should prompt to conduct further assessments using screening tools (e.g. MMSE score).

Addressing comorbidities. The number of comorbidities increases with age progression. Specific attention must be focused on so-called cognitive comorbidities. They relate in particular to cardiovascular diseases, cerebrovascular diseases, diabetes mellitus and OSAS. These should be treated according to current guidelines.

Pulmonary rehabilitation. Balance training and fall prevention strategies are not included in international guidelines for PR, and very few programs include standardized balance assessment. Although exercise can improve balance and decrease fall risk in older adults, interventions that include exercise to challenge balance have greater effects on fall risk and balance. Physical exercise training involving balance, strength training, movement speed and coordination has improved balance and frailty markers in multiple randomized and nonrandomized studies [87, 88]. Past cross-sectional research has provided support for the hypothesis that greater levels of aerobic fitness may be associated with a lessening of the normal age-related declines in cognitive functioning [89, 90]. It is conceivable that improvements in

cognitive functions such as executive function might help to improve self-management skills and potentially assist in sustaining the other substantial benefits of pulmonary rehabilitation.

Cognitive training. Given the increased prevalence of cognitive impairment in COPD and potentially devastating effects, a structured assessment of cognitive function should be implemented as a routine component of the evaluation of COPD patients. Those identified with a screening tool as possibly having MCI should be referred for further assessment to a psychiatrist. Identifying the coping styles in patients with COPD represents an important aspect of the individualized treatment of the patient. Interventions aiming at enhancing the problem- or emotion-focused coping may improve COPD prognosis [91].

Oxygen therapy: to whom? when? There is debate whether screening for cognitive impairment should be routinely applied. From the point of view of the hypoxemia approach, the answer to this debate will have to consider the evidence: (1) one in four people with COPD have cognitive impairment and over time, cognitive decline will deepen (risking an evolution toward multi-infarct dementia or Alzheimer disease) [92–94]. (2) It is now recognized that not only continuous, but also intermittent hypoxia (efforts, daily activities and sleep) can by repetition cause changes in brain neurochemistry and structure [7, 36]. (3) Cognitive impairment goes along with the severity of COPD, age and type/number of cognitive comorbidities. (4) Regular use of supplemental oxygen therapy has been shown to decrease the risk for cognitive impairment in patients with COPD [37, 38, 95].

Therefore, even the detection of intermittent desaturation (effort, daily activity and sleep), will have to lead to establishing earlier oxygen supplementation in order to prevent irreversible brain damage.

4. Conclusions

At least 40% of COPD patients present irreversible neuronal damage or dysfunction that is separate from other comorbidities. That is why cognitive impairment has to be listed in the first line of extrathoracic manifestations. Not identifying cognitive impairment we miss the fact that this condition may be a precursor to develop dementia in about a third of cases, or even higher in the context of COPD associated with other comorbidities. Cognitive impairment has been shown to increase the risk of hospitalization, disability and death. Hypoxemia is a serious problem that, even under the conditions of intermittent occurrence, should be sanctioned as early as possible by establishing LTOT. Besides oxygen therapy, the most effective therapeutic actions and strategies to these particular populations include: addressing comorbidities, pulmonary rehabilitation and cognitive training.

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