Chapter

Cognitive Impairment in Chronic Lung Diseases

Emanuela Tudorache, Monica Marc, Daniel Traila and Diana Manolescu

Abstract

The increase in life expectancy has been accompanied by an escalation of age-related disease incidence. Mild cognitive impairment (MCI) is a decline of cognitive function higher than expected for a certain age, but not severe enough to meet the criteria for dementia. Hypoxemia, smoking history, ageing and several comorbidities are risk factors for both chronic respiratory diseases and cognitive deficit. Up to 70% of patients with chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA) or idiopathic pulmonary fibrosis (IPF) have a form of cognitive impairment. Furthermore, a low neuropsychological performance is an independent predictor of disability and mortality in these populations. Efficient tools for cognitive assessment have been validated for these patients and should be used for better clinical outcomes. The physiopathological mechanisms, clinical impact and prevention strategies for cognitive dysfunction in chronic respiratory diseases will be detailed in the following chapter.

Keywords: cognitive dysfunction, hypoxemia, chronic obstructive pulmonary disease, obstructive sleep apnea, idiopathic pulmonary fibrosis

1. Introduction

In the era of antibiotics, vaccines and other medical innovations, life expectancy has increased worldwide, which has led to an enhanced prevalence chronic diseases. Only in the USA, the Department of Health and Human Services estimates that by the year 2040, 82.3 million Americans (21.7% of the population) will be over 65 years of age [1]. Consequently, age-related illnesses that cause a significant morbidity and mortality will become a rising public health problem. At the same time, there is an increase in the prevalence of multimorbidity, defined by the coexistence of two or more chronic pathologies in the same individual. Studies show that in individuals that are over 60 years old, the multimorbidity range is from 55 to 98% [2]. Multimorbidity is associated with functional decline, disability, poor quality of life, higher emergency care and hospitalizations rates, polypharmacy and increased healthcare costs, all of which are a great burden for society [3].

The concept of cognitive impairment has been carefully analysed in the last two decades, given the devastating consequences of this problem, mainly among elderly populations. Cognitive function can be divided into six large domains: language (verbal fluency and comprehension), learning ability and memory (work memory and memory-based tagging), attention, executive functions (planning and problem

solving), praxis (motor-ideative, ideative and visual constructive) and visuospatial function [4].

Mild cognitive impairment (MCI) is defined as a cognitive dysfunction more severe than normal age-related cognitive decline or education level, but not severe enough to significantly interfere with daily function [5]. MCI exceeds the "age-related" decline in cognition healthy individuals experience but does not meet the criteria for dementia. Furthermore, not all cases of MCI will progress towards dementia.

In the general population, studies have shown a prevalence of MCI between 10 and 20% in older adults [5]. However, cognitive impairment is heavily underdiagnosed and undertreated by primary care physicians. There are several screening tools that can identify those with a high risk of MCI such as the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Saint Louis University Mental Status Examination (SLUMS) or Rapid Cognitive Screen. Once the diagnosis of cognitive dysfunction is determined, it is essential to establish the aetiology and the contributing factors and to evaluate if there are any reversible causes. Every practitioner should be familiar with these questionnaires, especially MMSE, and should use them whenever they suspect a person of MCI.

Neuroanatomical structures and their function can be assessed by neuroimaging techniques. Computed tomography (CT) scan and magnetic resonance imaging (MRI) can analyse the brain structure and exclude conditions such as strokes, brain tumours or vascular malformation. The fluorodeoxyglucose positron-emission tomography (FDG-PET) scan, mostly used for research purposes, can evaluate the brain function and seems to be more sensitive than MRI in MCI diagnosis. This tool uses a radioactive glucose tracer which binds to highly active brain areas. The presence of hypometabolic areas in the temporal or parietal lobe is a sign of neurodegeneration. Subjects who develop these hypometabolic areas have a higher risk of progression from MCI to dementia [6, 7]. For research purposes, there are several biomarkers used for the diagnosis of MCI and dementia, but the lack of standardization regarding optimal cutoff points limits their clinical utility [8].

There are well-established risk factors for developing MCI: age, male gender, family history of cognitive impairment, the presence of the apolipoprotein E allele, smoking and low educational level [9]. Moreover, one study, which aimed to determine if multimorbidity could be a risk factor for mild cognitive impairment and dementia, found that individuals who associate at least two of the following, hypertension, hyperlipidemia, coronary artery disease and arthritis, had a very high risk of MCI [3].

Recent studies showed that some chronic respiratory conditions, such as chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA) or idiopathic pulmonary fibrosis (IPF), have an important impact on cognitive function. There are discrepancies regarding the reported prevalence of cognitive dysfunction among the conditions listed above, which can be explained by study design and limitations: diagnostic methods for cognitive impairment (psychometric tools or neuroimaging), small sample size or inappropriate control group, assessment moment (stable phase/exacerbation), the severity of the airflow limitation, presence of hypoxia and the use of long-term oxygen therapy. Multiple confounders can also contribute to the large variation of data regarding prevalence: age, education level, smoking history, comorbidities, etc.

2. Cognitive impairment in obstructive sleep apnea

Sleep apnea syndrome is a disorder of breathing during sleep, characterized by total or partial obstruction of the upper airways leading to hypoxia and

hypercapnia, plus increased respiratory effort [10]. These features produce micro-awakenings that result in disruption of sleep and changes in neuronal activity. All of these are potential mechanisms for cognitive deficiency [11].

In adults, the prevalence of OSA increases significantly with age. Between 30 and 49 years, 10% of men and 3% of women are diagnosed, increasing to 17 and 9%, respectively, for 50–70 years [12] and with increasing prevalence among postmenopausal women [13]. These percentages are higher than those published 10 years ago, due to the fact that obesity is increasing among the population of developing countries [14]. More worryingly, the true prevalence may be underestimated as many people with OSA remain undiagnosed.

Nighttime symptoms are noisy snoring, non-restful sleep, nocturia, sweating and dry mouth. One of the most common daytime symptoms in patients with OSA is daytime sleepiness. This greatly influences the quality of life and cognitive performance.

OSA has been associated with a wide range of psychological problems such as depression, anxiety, neurocognitive dysfunction, especially attention, alertness, memory and learning, phenomena due to fragmentation of sleep and intermittent hypoxemia [15–17]. Fragmentation of sleep, sleep deprivation and the association of excessive daytime sleepiness are proposed mechanisms that underlie cognitive impairment through their impact on attention [18, 19].

The exact prevalence of cognitive disorders and their severity due to multiple comorbidities with which this syndrome is associated is not known in adult patients with OSA.

2.1 Risk factors for cognitive deficits in OSA patients

There are numerous OSA comorbidities that can influence cognitive function, such as treatment-resistant hypertension [20], diabetes [21], COPD, congestive heart failure, strokes [22], smoking [23] and alcoholism [24]. Also age, sex (male), obesity and the use of psychoactive drugs are considered independent risk factors [25].

Ageing itself causes decline in cognitive function, and the presence of OSA in these patients leads to further brain injury, with cognitive impairment being more obvious [26]. It is also known that smoking, through its damaging effects on blood vessels and circulation, increases the risk of dementia, both vascular and Alzheimer's, as well as neurocognitive decline not associated with dementia [27].

Another important factor in the association of OSA with cognitive decline is, it seems, the genetic factor. Thus, studies show that the presence of apolipoprotein E4 (ApoE4) is associated with an increased incidence of cognitive disorders [28].

High blood pressure is associated with cognitive decline, both when isolated and in the presence of metabolic syndrome, especially due to the presence of cardiovascular risk factors [29].

Also, the presence of hypothyroidism in patients with OSA may accelerate cognitive decline, and current data are not sufficient to demonstrate whether the treatment ameliorates the decline phenomena [30].

Moderate alcohol consumption may protect against dementia, but significant alcohol consumption is associated with cognitive impairment, which is manifested by loss of memory, impaired personality and impaired judgement [24]. Alcohol intake before bedtime affects sleep architecture [31]. In addition, depending on the quantity, the instability of the upper airways may increase [32]. Thus, excessive alcohol use by patients with OSA may lead to more severe cognitive deficits.

Another common comorbidity of OSA is stroke, which, independently, is accompanied by a cognitive deficiency and even dementia. Studies show that up

to 30% of patients with stroke can develop dementia [33, 34]. And psychoactive medication, e.g. benzodiazepines, narcotics and barbiturates, can aggravate OSA and increase attention and alertness problems [35, 36].

Studies carried out over time have shown structural and functional changes in the brain, resulting in cognitive deficiency. There are studies that, by MRI techniques, have shown decrease of grey matter in the hippocampus; cerebellum; frontal, parietal and temporal lobes; as well as the anterior cingulate cortex [37–39]. Also, a decrease in the hippocampus was observed, which plays an important role in memory consolidation. The white matter changes reported by O'Donoghue et al. indicate that axonal or glial pathology is also present in OSA, consistent with other previous findings [40].

2.2 Physiopathology of cognitive impairment in patients with OSA

Studies on the cardiovascular effects of OSA have shown that the disorder results in changes in vascular structure and function, these changes being frequently encountered in other hypoxic populations [41]. It is assumed that hypoxia would have a direct effect on the neuropsychic in patients with OSA, with existing similar mechanisms in terms of cardiovascular changes and brain vessels. Hypoxia produces immediate vasodilation, being a protective mechanism to more efficiently distribute oxygen to the affected organ. Studies have shown that this protective mechanism does not exist in patients with OSA [42]. One potential reason why these patients do not have a response to hypoxemia is because they suffer from repeated episodes of hypoxemia (over five events/h) and desaturation, not just a sustained hypoxic event. Thus, the post-episode recovery time being limited, it is not possible to estimate whether there is a protective response to recurrent hypoxic events, but it is assumed that the vessels would suffer [43].

Therefore, in patients with OSA, there are lesions due to hypoxia and reperfusion with increased lipid peroxidation. This process involves the oxidation of polyunsaturated fatty acids with the formation of reactive oxygen species and toxic products, having potential damaging effects for the brain and heart.

Also, in patients with vascular pathology, endothelial dysfunction is present. In patients with OSA, imbalances between vasoconstrictive mediators (higher thromboxane and endothelin levels) and vasodilators (nitric oxide, prostacycline) appear, and nitric oxide production has been shown to decrease in OSA. This imbalance predisposes to atherosclerosis [44]. Thus, the effects on cerebral flow, as well as hypoxia, may cause the onset of cerebral infarctions, resulting in vascular dementia. The presence of endothelial dysfunction, with the onset of neurocognitive deficits, has been described even in studies performed in the paediatric population [16].

There are authors who consider that the cognitive impairment in OSA represents the short-term consequence of the poor quality of sleep manifested by daytime sleepiness or attention difficulties. Studies have shown specific and localized frontal lobe involvement, responsible for the executory dysfunction observed in OSA [45]. The basis of this hypothesis is that sleep disruption reduces the efficiency of restoration processes in the prefrontal cortex that will also lead to cellular and biochemical stress. These processes, in turn, disrupt functional homeostasis, altering the viability of neuronal and glial cells [46–48]. The severity of sleep fragmentation is associated with attention deficit and decreased alertness, and the overall cognitive deficit is the consequence of hypoxia. Due to sleep fragmentation, alteration of blood gases and changes of homeostasis in the frontal lobe and hippocampus leads to memory impairment and executory function deficiency.

2.3 The effects of CPAP therapy on cognitive deficiency

A direct consequence of OSA, with impact on both personal and social levels, is the loss of vigilance. This increases the risk of traffic accidents in untreated patients, which is why it is important to diagnose and treat this condition as early as possible [49]. Election treatment of OSA is continuous positive airway pressure (CPAP) therapy. This method was first described in 1981 [50]. Since then, technological progress has been made to suit the needs of patients. Also, in order to improve treatment adherence, device manufacturers have considered the importance of producing mask interfaces that match the user's physiognomy. This variety improves comfort and reduces air leakage. The use of CPAP for at least 4 h of sleep during a 24-h period defines a minimum acceptable level in terms of a beneficial therapeutic response. Thus, for maximum benefit, most clinicians recommend using the device for the entire duration of sleep [51].

Canessa et al. studied the effects of CPAP therapy on neurocognitive changes in 17 OSA patients. Therefore, voxel-based morphometry determinations showed significant post-therapy improvements in the cognition level, together with the increase of the volume of the grey matter in the frontal lobe and hippocampus [52]. This is why early diagnosis and initiation of CPAP therapy could prevent, in the medium and long term, the cognitive impairment. In summary, this study provides the first evidence that structural brain abnormalities exist in hypoxemia-sensitive regions and they may change with treatment. These results suggest that even the negative neurological effects of hypoxemia can be reversed with consistent and complete treatment. Therefore, adherence to CPAP treatment can lead not only to clinical recovery but also to structural brain recovery. It should be noted that the patients in this study showed a positive response to treatment. MRI may thus be used as a marker, to evaluate the response to treatment [53].

There are studies that show that use of CPAP over 12 months also leads to significant recovery of the impaired white matter, including corpus callosum, with important impact on improving cognition [54]. There are also numerous studies evaluating the effects of CPAP therapy in stroke patients who develop OSA. The stroke can aggravate functional changes and cognition. A study conducted in Korea highlights the beneficial effects of the therapy and suggests that this treatment should be considered as part of the rehabilitation programme for stroke patients. Thereby, CPAP therapy applied to patients with subacute stroke for a relatively short period of time leads to an improvement in sleep quality, daytime sleepiness and cognitive function. Further research regarding the improvement of neurological and functional status among stroke patients, who have received long-term CPAP treatment, is needed [55].

In conclusion, although there are numerous studies that have focused on the association of OSA with cognitive deficits, things are far from fully elucidated. Variate and numerous comorbidities, including ageing, hypoxemia, genetic factors, strokes, etc., independently influence these deficits. Untreated OSA is correlated with changes in brain structure and function through cell death, grey matter destruction, inflammatory changes and decreased white matter integrity. Unlike other pathologies, however, initiating CPAP therapy as early as possible prevents the installation of the cognitive deficiency or improves it if it is already installed.

3. Cognitive impairment in chronic obstructive pulmonary disease

COPD is a common disease, characterized by persistent respiratory symptoms and airflow limitation caused by significant exposure to noxious particles and gases.

COPD is an important cause of morbidity and premature death. According to the WHO, by 2030 it will be the third cause of death worldwide [56].

A large meta-analysis which included 23,116 patients with COPD showed an alarming prevalence of MCI, up to 32%, compared with the prevalence of 10–20% in the general population [57]. Furthermore, in time this mild cognitive decline seems to aggravate, and these patients will have an increased risk to develop multi-infarct dementia or Alzheimer's disease [58].

3.1 Risk factors for cognitive impairment in patients with COPD

The origin of the cognitive impairment COPD patients is still not well established. Several pathological relays can interfere: smoking, ageing, severe lung disease, hypoxemia, hypercapnia, systemic inflammation, oxidative stress, endothelial dysfunction, comorbidities, sedentary lifestyle and genetic factors.

3.2 Physiopathology of cognitive impairment in patients with COPD

From all the above, hypoxemia seems to be the most important risk factor. Not only continuous hypoxemia but also the intermittent one (during efforts, sleep and daily activities) can cause brain damage [59]. Moreover, a study showed that during COPD exacerbations when hypoxemia worsens, patients have significantly altered cognitive scores compared with those recorded in stable phases and age-matched controls [60]. Neurologic impairment also worsens with COPD progression. In the severe pulmonary disease, altered MMSE scores were reported in 64% of cases [61]. The most common abnormalities in the MMSE included construction (39%), attention (31%), verbal recall (26%), visuospatial orientation (24%) and language (13%). In tasks that required drawing (e.g. an analogue clock with a set time) or other tasks that required judgement, poor performance was associated with a higher mortality [62]. In addition, Chang et al. in a 3-year prospective study showed that the association between COPD and cognitive dysfunction led to increased disability, hospital rate and mortality [63].

One of the most elaborate studies was performed by Dodd et al. [4] who focused on non-hypoxemic COPD patients and combined different brain function assessment techniques such as magnetic resonance diffusion tensor imaging, resting state functional MRI and neuropsychological questionnaires. The report showed that these individuals had decreased integrity of the white matter, dysfunction of grey matter and poor performance in the cognitive questionnaires, compared with age-matched controls. The most significant deficits recorded through imaging techniques were poor executive function, low processing speed and episodic and working memory impairment, which all corresponded with the deficits seen on the MMSE test.

The Rotterdam Study used high-resolution MRI to evaluate cerebral structures in subjects with COPD and reported a higher frequency of cerebral microbleeds. This observation supports the concept of cerebral small-vessel disease that leads to cognitive decline via cerebral micro-bleeding areas. They also increased the MRI performance by introducing voxel-based morphometry analysis. Through this technique, they demonstrated for the first time that even stable COPD patients, who had subclinical cognitive impairment, presented grey matter volume alterations on MRI [64].

Other MRI studies revealed a significantly loss of grey matter in numerous brain areas: precuneus, right inferior parietal lobule, right superior temporal gyrus/middle temporal gyrus, hippocampus, limbic and paralimbic structures, cingulate, amygdala, etc. The common aspect in these studies is heterogeneity and broad

distribution of the lesions which could explain the multiple and variate neurologic manifestations these patients experience. Moreover, neuroimaging showed that parietal lobule and precuneus are also altered in Alzheimer's disease.

The psychometric profile impairment correlates with variable components of COPD such as disease severity, exacerbations, hypoxemia or hypercapnia [58]. For accurate results it is indicated to use a battery of tests, not a single one. The most commonly affected cognitive domains are memory, attention, motor and executive function, naming ability and visuospatial orientation [65].

On the other hand, COPD cases without comorbidities are rare. This disease is frequently associated with both respiratory pathologies, like pulmonary hypertension (3–84%), obstructive sleep apnea (58–88%) or lung cancer (3–22%), and non-respiratory comorbidities such as systemic arterial hypertension (14–71%), ischemic heart disease (4–68%), depression (12–49%) and diabetes mellitus type 2 (10–33%) [66]. Although the number of comorbidities rises with age, special caution should be addressed to cognitive-related comorbidities: cerebrovascular diseases, cardiovascular pathology, diabetes mellitus and sleep apnea syndrome. These pathologies should be managed according to current guidelines.

3.3 The effects of therapy and pulmonary rehabilitation on cognitive deficiency in COPD patients

Studies show that 50% of COPD patients abandon the prescribed inhaled medication and the oxygen therapy during the first year of therapy and just 25% use oxygen therapy for activities outside their house [67]. Moreover, older COPD patients and those with cognitive impairment have even lower adherence levels to inhalation therapy. The cognitive status impacts patient's ability to recall when and how to use the inhaler devices. Poor executive functioning is often associated with a "knowing–doing" discrepancy [68]. All these factors listed above have a negative impact on treatment adherence and self-management.

The dyspnea–inactivity–muscular dysfunction circle developed by COPD patients will lead to isolation, depression and low adherence to pulmonary rehabilitation programmes. Given the multifactorial aspects of adherence and the high prevalence of MCI among COPD population, pulmonary rehabilitation programmes should be tailored to subject's needs.

On the other hand, these programmes have a positive feedback on respiratory symptoms and neurologic function. Therefore, screening for these comorbidities should be considered during baseline pulmonary rehabilitation assessment [69]. Cognitive behavioural therapy or psychological support should be considered when psychological difficulties interfere with disease self-management and adherence [67].

Another condition that should not be ignored in patients with COPD is gait impairment. More evidence suggests that muscle loss, reduced exercise capacity and functional mobility is leading to an important risk of falls. Interventions that include coordination, balance and strength training proved to be effective in older adults [70]. However, balance training and fall prevention strategies are still not mentioned by the pulmonary rehabilitation guidelines, and very few rehabilitation centres have a standardized balance assessment.

Although regular use of long-term oxygen therapy (LTOT) is correlated with a reduced risk of cognitive impairment in subjects with COPD, it is still under debate when and to whom it should be addressed. However, in patients who develop intermittent hypoxemia (during effort or sleep), earlier oxygen supplementation should be considered in order to prevent irreversible neurologic damage [56].

During COPD exacerbations in hypercapnic respiratory failure, non-invasive ventilation is a key management tool which markedly reduces mortality and morbidity. Prompt initiation of CPAP therapy prevents the installation of the cognitive impairment [71].

4. Cognitive impairment in idiopathic pulmonary fibrosis

Pulmonary fibrosis describes the group of fibrosing interstitial lung diseases (ILDs) that causes progressive scarring of the alveolar interstitium, often leading to hypoxemic respiratory failure. ILDs encompass a large and varied group of parenchymal lung disorders, including diseases of unknown cause (idiopathic interstitial pneumonias), as well as those associated with other diseases (connective tissue disease-associated ILDs, chronic sarcoidosis) or environmental exposures (chronic hypersensitivity pneumonitis).

Idiopathic pulmonary fibrosis (IPF), the most extensively studied type of ILD, is a relentlessly progressive lung disease with a prognosis that can be worse than many cancers. With a median survival time of 2.5–3.5 years after diagnosis [72], IPF portends substantial morbidity and mortality outcomes, not all of which are directly related to the progressive fibrotic disease itself.

This older population with a median age of 66 years at diagnosis frequently experience various comorbidities, which influence the clinical spectrum, progression and mortality of the disease. An analysis of 272 IPF patients reported that 58% of cases had one, two or three comorbid conditions, 30% had four to seven comorbid conditions and only 12% had no comorbidities [73]. Respiratory comorbidities, including emphysema (8–34%), obstructive sleep apnea (58–88%), lung cancer (3–22%) and pulmonary hypertension (3–84%), were common in many studies, although estimates vary widely depending on the source population. Non-respiratory comorbidities such as gastro-oesophageal reflux (30–80%), systemic arterial hypertension (14–71%), ischaemic heart disease (4–68%), diabetes mellitus type 2 (10–33%) and depression (12–49%) are also highly prevalent [74, 75].

4.1 Risk factors for cognitive deficits in patients with IPF

Related to IPF or associated morbidity, there are several potential factors and conditions for the emergence of a cognitive deficit. Hypoxemia, a history of smoking, ageing and chronic evolution of the disease are potential elements for the emergence of a cognitive deficit.

Difficulties in breathing (increased intrinsic elastic load of respiratory muscles and stimulation of peripheral mechanoreceptors) [76], night cough, drugs, hypoxemia and obstructive apnea can all alter the quality of life.

4.2 Physiopathology of cognitive impairment in patients with IPF

IPF patients develop progressive ventilatory restriction and exercise intolerance. Alteration of blood gases is a common feature in IPF pathophysiology. Patients experience transient or continuous hypoxia resulting in a substantial cumulative time with an SpO_2 below 90%. Nocturnal hypoxia is common in chronic fibrotic interstitial lung diseases, both in patients who associate OSA, as those without this comorbidity. In the absence of OSA, nocturnal hypoxia could be a result of alveolar hypoventilation, altered ventilation-perfusion ratio and a desaturation trend, due to patients on the abrupt portion of the oxygen-haemoglobin dissociation curve [77, 78].

Epidemiologic research has shown that besides genetic and environmental factors, such as lifestyles and cardiovascular risk factors, decreased lung function is also associated with dementia and cognitive impairment in the general population.

In a large population-based cohort enrolled in the Atherosclerosis Risk in Communities Study [79], the presence of a restrictive ventilatory pattern was associated with worse performance in cognitive assessments and with an increased risk of dementia hospitalization.

A recent prospective study [80] found that patients with restrictive lung disease have almost twice the chance of developing dementia or mild cognitive impairment as healthy individuals. Researchers followed more than 14.000 middle-aged people for over 23 years. Lung disease and impaired lung function were associated with greater risk of dementia and mild cognitive impairment through both Alzheimer's disease and cerebrovascular aetiologies. Although both COPD and restrictive impairment were associated with increased risk of the dementia phenotypes, magnitudes of association were most pronounced for restrictive impairment. There were no differences between smokers and non-smokers.

Different pathogenic mechanisms could explain the association of lung function with cognitive performance and risk of dementia. Chronic hypoxia might lead to ischaemic brain injury and neurodegeneration as prospective studies have found that individuals with low lung function or reduced arterial oxygen saturation are more likely to develop white matter lesions and lacunar infarcts [81, 82].

A restrictive ventilatory pattern has been associated with the incidence of diabetes and subclinical atherosclerosis and an increased risk of cardiovascular outcomes [83, 84]. In turn, diabetes and cardiovascular disease might cause cognitive impairment and increase the risk of dementia.

Worse lung function might cause cognitive impairment and dementia through the development of a pro-inflammatory state. High levels of C-reactive protein, elevated in individuals with reduced lung function, have been associated with a higher risk of dementia [85, 86].

In IPF, a disease with a potential rapid and frequent development of hypoxemia, it is surprising that cognitive impairment has been investigated in very few studies.

In a limited study [87], with only seven IPF patients undergoing pulmonary rehabilitation, applying a battery of five psychometric tests (recall of verbal information, sustained visual attention, efficiency in completing sequential tasks, verbal fluency, visuospatial and graphomotor proficiency) found impaired cognition only on the level of visual attention.

A prospective, observational study examining cognitive function in 30 IPF patients with normal oxygen saturations and comparing them to COPD and smoking controls demonstrated that almost half of IPF patients have mild cognitive dysfunction, unexplained by age [88].

In a prospective, cross-sectional, descriptive study [89], Bors et al. showed that individuals with severe IPF have worse cognitive function than those with mild-to-moderate disease and controls. Participants were evaluated through five neuropsychological tests that assessed various domains of cognitive function: speed for attention, sequencing, mental flexibility, visual search and motor function, information processing speed, selective attention, cognitive flexibility, executive function, assessment of verbal recall and recognition and specific cognitive deficits related to accessibility of lexical and semantic information. Severe IPF patients had a significantly inferior performance on tasks requiring speed-divided attention and slower processing speeds when requiring suppression of a familiar response. They are also more likely to have poorer health-related quality of life and symptoms of depression.

A cross-sectional study aimed to assess cognition in IPF and to identify clinical cognition modifiers, and 23 IPF patients were evaluated using the Montreal Cognitive Assessment (MoCA) [66]. As it has been previously mentioned, MoCA is a screening instrument with high specificity and sensitivity for detecting early cognitive impairments and is validated in multiple settings and disorders. MoCA evaluates several cognitive domains (short-term memory, visuospatial abilities, executive functioning, attention, concentration and working memory, language, orientation to time and place) to differentiate healthy cognitive ageing from mild cognitive impairment [90]. The study found a mild cognitive impairment in patients with IPF that is related to the areas of visuospatial abilities, language and working memory. Obstructive sleep apnea was highly prevalent in these patients (more than 80% of cases), and there was a significant correlation between cognitive function and the severity of apnea hypopnea index. Poor sleep quality is frequently met in IPF through sleep breathing disorders, including OSA, implying increased sleep fragmentation, decreased slow wave and REM sleep, as well as sleep oxygen desaturation [91].

4.3 Management of cognitive deficiency in IPF patients

Health-related quality of life is especially important in this patient population, given the lack of treatment options, poor mortality and rapid progression of the disease. The morbidity associated with IPF has a wide and profound impact on the patient's quality of life. Therefore, cognition level and other patient-centred outcomes are important goals to be evaluated in clinical research and practice. For IPF we do not currently have a specific cognitive assessment tool, so researchers have used validated tools in cognition analysis of other chronic respiratory diseases. The potential problem is that these tools cannot capture many of the effects of IPF on patients' lives.

5. Conclusion

Patients with chronic respiratory conditions, such as obstructive sleep apnea, chronic obstructive pulmonary disease or idiopathic pulmonary fibrosis, commonly associate cognitive impairment. Neurologic assessment should be included in the routine diagnostic algorithm of these conditions, in order to appreciate the overall impact of the disease, on patient's quality of life and prognosis. Physicians who notice signs of memory loss, disorientation, gait impairment or even poor adherence to pharmacologic/nonpharmacologic treatment, should screen their patients for cognitive dysfunction. For a better outcome, subjects who are identified with mild cognitive impairment by a screening tool should be referred for a thorough evaluation to a neurologist, and the chronic lung disease management should be tailored according to individual's needs.

DOI: http://dx.doi.org/10.5772/intechopen.91825

Author details

Emanuela Tudorache[1*], Monica Marc[1], Daniel Traila[1] and Diana Manolescu[2]

1 Department of Pulmonology, "Victor Babes" University of Medicine and Pharmacy, Timişoara, Romania

2 Department of Radiology, "Victor Babes" University of Medicine and Pharmacy, Timişoara, Romania

*Address all correspondence to: tudorache_emanuela@yahoo.com

References

[1] http://www.acl.gov/sites/default/files/about-acl/2017-03/FY15OAAReportCongress_2017-1-24.docx

[2] Marengoni A, Roso-Llorach A, Vetrano DL, et al. Patterns of multimorbidity in a population-based cohort of older people: Sociodemographic, lifestyle, clinical, and functional differences. The Journals of Gerontology Series A Biological Sciences. 9 March 2020;**75**(4):798-805. DOI: 10.1093/gerona/glz137

[3] Vassilaki M, Aakre JA, Cha RH, et al. Multimorbidity and risk of mild cognitive impairment. Journal of the American Geriatrics Society. 2015;**63**(9):1783-1790

[4] Dodd JW, Chung AW, van den Broek MD, et al. Brain structure and function in chronic obstructive pulmonary disease: A multimodal cranial magnetic resonance imaging study. American Journal of Respiratory and Critical Care Medicine. 2012;**186**(3):240-245

[5] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013

[6] Yuan Y, Gu ZX, Wei WS. Fluorodeoxyglucose-positron-emission tomography, single-photon emission tomography, and structural MR imaging for prediction of rapid conversion to Alzheimer disease in patients with mild cognitive impairment: A meta-analysis. AJNR. American Journal of Neuroradiology. 2009;**30**:404-410

[7] Karow DS, McEvoy LK, Fennema-Notestine C, et al. Relative capability of MR imaging and FDG PET to depict changes associated with prodromal and early Alzheimer disease. Radiology. 2010;**256**:932-942

[8] Sanford AM. Mild cognitive impairment. Clinics in Geriatric Medicine. 2017;**33**(3):325-337

[9] Ng TP, Feng L, Nyunt MS, et al. Metabolic syndrome and the risk of mild cognitive impairment and progression to dementia: Follow-up of the Singapore Longitudinal Ageing Study Cohort. JAMA Neurology. 2016;**73**(4):456-463

[10] Edwards BA, Eckert DJ, Jordan AS. Obstructive sleep apnoea pathogenesis from mild to severe: Is it all the same? Respirology. 2016;**22**:33-42

[11] EEG arousals: Scoring rules and examples. A preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep. 1992;**15**:173-184

[12] Peppard PE, Young T, Barnet JH, et al. Increased prevalence of sleep disordered breathing in adults. American Journal of Epidemiology. 2013;**117**:1006-1014

[13] Kapsimalis F, Kryger M. Sleep breathing disorders in the U.S. female population. Journal of Women's Health (Larchmt). 2009;**18**:1211-1219

[14] Senaratna CV, Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. Sleep Medicine Reviews. 2017;**34**:70-81

[15] Salorio CF, White DA, Piccirillo J, et al. Learning, memory, and executive control in individuals with obstructive sleep apnea syndrome. Journal of Clinical and Experimental Neuropsychology. 2002;**24**(1):93-100

[16] Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: Towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. Journal of Sleep Research. 2002;**11**(1):1-16

[17] Sutton AM. Executive functioning in the presence of sleep disordered breathing. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2008;**69**(1-B):701

[18] Verstraeten E, Cluydts R. Executive control of attention in sleep apnea patients: Theoretical concepts and methodological considerations. Sleep Medicine Reviews. 2004;**8**(4):257-267

[19] Verstraeten E, Cluydts R, Pevernagie D, et al. Executive function in sleep apnea: Controlling for attentional capacity in assessing executive attention. Sleep. 2004;**27**(4):685-693

[20] Logan AG, Perlikowski SM, Mente A, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. Journal of Hypertension. 2001;**19**(12):2271-2277

[21] Elmasry A, Lindberg E, Berne C, et al. Sleep-disordered breathing and glucose metabolism in hypertensive men: A population-based study. Journal of Internal Medicine. 2001;**249**(2):153-161

[22] Parra O, Arboix A, Bechich S, et al. Time course of sleep related breathing disorders in first-ever stroke or transient ischemic attack. American Journal of Respiratory and Critical Care Medicine. 2000;**161**(2 pt 1):375-380

[23] Wetter DW, Young TB, Bidwell TR, et al. Smoking as a risk factor for sleep-disordered breathing. Archives of Internal Medicine. 1994;**154**(19):2219-2224

[24] Chan KK, Chiu KC, Chu LW. Association between alcohol consumption and cognitive impairment in Southern Chinese older adults. International Journal of Geriatric Psychiatry. 2010;**25**(12):1272-1279

[25] Lal C, Strange C, Bachman D. Neurocognitive impairment in obstructive sleep apnea. Chest. 2012;**141**(6):1601-1610

[26] Petersen RC, Roberts RO, Knopman DS, et al. The Mayo Clinic Study of Aging . Prevalence of mild cognitive impairment is higher in men. Neurology. 2010;**75**(10):889-897

[27] Bekris LM, Yu CE, Bird TD, et al. Genetics of Alzheimer disease. Journal of Geriatric Psychiatry and Neurology. 2010;**23**(4):213-227

[28] Kadotani H, Kadotani T, Young T, et al. Association between apolipoprotein E epsilon4 and sleep-disordered breathing in adults. The Journal of the American Medical Association. 2001;**285**(22):2888-2890

[29] Panza F, Frisardi V, Capurso C, et al. Metabolic syndrome and cognitive impairment: Current epidemiology and possible underlying mechanisms. Journal of Alzheimer's Disease. 2010;**21**(3):691-724

[30] Lin CC, Tsan KW, Chen PJ. The relationship between sleep apnea syndrome and hypothyroidism. Chest. 1992;**102**(6):1663-1667

[31] Feige B, Gann H, Brueck R, et al. Effects of alcohol on polysomnographically recorded sleep in healthy subjects. Alcoholism, Clinical and Experimental Research. 2006;**30**(9):1527-1537

[32] Issa FG, Sullivan CE. Upper airway closing pressures in snorers. Journal of Applied Physiology. 1984;**57**(2):528-535

[33] Minoguchi K, Yokoe T, Tazaki T, et al. Silent brain infarction and platelet activation in obstructive sleep apnea. American Journal of Respiratory and Critical Care Medicine. 2007;**175**(6):612-617

[34] Tatemichi TK, Foulkes MA, Mohr JP, et al. Dementia in stroke survivors in the Stroke Data Bank cohort. Prevalence, incidence, risk factors, and computed tomographic fi ndings. Stroke. 1990;**21**(6):858-866

[35] Moore AR, O'Keeffe ST. Drug-induced cognitive impairment in the elderly. Drugs & Aging. 1999;**15**(1):15-28

[36] Shirani A, Paradiso S, Dyken ME. The impact of atypical antipsychotic use on obstructive sleep apnea: A pilot study and literature review. Sleep Medicine. 2011;**12**(6):591-597

[37] Gale SD, Hopkins RO. Effects of hypoxia on the brain: Neuroimaging and neuropsychological findings following carbon monoxide poisoning and obstructive sleep apnea. Journal of the International Neuropsychological Society. 2004;**10**(1):60-71

[38] Macey PM, Henderson LA, Macey KE, et al. Brain morphology associated with obstructive sleep apnea. American Journal of Respiratory and Critical Care Medicine. 2002;**166**(10):1382-1387

[39] Morrell MJ, McRobbie DW, Quest RA, et al. Changes in brain morphology associated with obstructive sleep apnea. Sleep Medicine. 2003;**4**(5):451-454

[40] O'Donoghue FJ, Wellard RM, Rochford PD, et al. Magnetic resonance spectroscopy and neurocognitive dysfunction in obstructive sleep apnea before and after CPAP treatment. Sleep. 2012;**35**:41-48

[41] Parkinson J, Dalley J, Cardinal R, et al. Nucleus accumbens dopamine depletion impairs both acquisition and performance of appetitive Pavlovian approach behaviour: Implications for mesoaccumbens dopamine function. Behavioural Brain Research. 2002;**137**(1-2):149-163

[42] Kato M, Roberts-Thomson P, Phillips BG, et al. Impairment of endothelium dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. 2000;**102**(21):2607-2610

[43] Aloia MS, Ardet JT, Davis JD, et al. Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome: A critical review. Journal of the International Neuropsychological Society. 2004;**10**:772-785

[44] Nedeljkovic ZS, Gokce N, Loscalzo J. Mechanisms of oxidative stress and vascular dysfunction. Postgraduate Medical Journal. 2003;**79**(930):195-199

[45] Gozal D, Kheirandish-Gozal L, Bhattacharjee R, et al. Neurocognitive and endothelial dysfunction in children with obstructive sleep apnea. Pediatrics. 2010;**126**(5):e1161-e1167

[46] Horne JA. Why We Sleep. Oxford: Oxford University Press; 1988

[47] Madsen PL. Blood flow and oxygen uptake in the human brain during various states of sleep and wakefulness. Acta Neurologica Scandinavica. 1993;**148**:S3-S27

[48] Maquet P. Sleep function (s) and cerebral metabolism. Behavioural Brain Research. 1995;**69**:75-83

[49] Findley LJ, Levinson MP, Bonnie RJ. Driving performance and automobile accidents in patients with sleep apnea. Clinics in Chest Medicine. 1992;**13**(3):427-435

[50] Sullivan CE, Issa FG, Berthon-Jones M, et al. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet. 1981;**1**(8225):862-865

[51] Antic NA, Catcheside P, Buchan C, et al. The effect of CPAP in normalizing daytime sleepiness, quality of life, and neurocognitive function in patients with moderate to severe OSA. Sleep. 2011;**34**(1):111-119

[52] Canessa N, Castronovo V, Cappa SF, et al. Obstructive sleep apnea: Brain structural changes and neurocognitive function before and after treatment. American Journal of Respiratory and Critical Care Medicine. 2011;**183**(10):1419-1426

[53] Rosenzweig I, Glasser M, Crum WR, et al. Changes in neurocognitive architecture in patients with obstructive sleep apnea treated with continuous positive airway pressure. EBioMedicine. 2016;**7**:221-229

[54] Castronovo V, Scifo P, Castellano A, et al. White matter integrity in obstructive sleep apnea before and after treatment. Sleep. 2014;**37**(9):1465-1475. DOI: 10.5665/sleep.3994

[55] Kim H, Im S, Park J i, et al. Improvement of cognitive function after continuous positive airway pressure treatment for subacute stroke patients with obstructive sleep apnea: A randomized controlled trial. Brain Sciences. 2019;**9**:252

[56] GOLD. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: 2019 Report. 2019. Available from: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf

[57] Yohannes AM, Chen W, Moga AM, et al. Cognitive impairment in chronic obstructive pulmonary disease and chronic heart failure: A systematic review and meta-analysis of observational studies. Journal of the American Medical Directors Association;**18**(5):451.e1-451.e11

[58] Oancea C, Tudorache E, Tudorache V. Neurocognitive impairment as systemic effects of COPD. In: McCarthy C, editor. COPD—An Update in Pathogenesis and Clinical Management. 2018;67-86. DOI: 10.5772/intechopen.70580

[59] Crişan AF, Oancea C, Timar B, et al. Cognitive impairment in chronic obstructive pulmonary disease. PLoS One. 2014;**9**(7):e102468

[60] Incalzi RA, Gemma A, Marra C, et al. Chronic obstructive pulmonary disease. An original model of cognitive decline. The American Review of Respiratory Disease. 1993;**148**(2):418-424

[61] Ozge C, Ozge A, Unal O. Cognitive and functional deterioration in patients with severe COPD. Behavioural Neurology. 2006;**17**(2):121-130

[62] Antonelli-Incalzi R, Corsonello A, Pedone C, et al. Drawing impairment predicts mortality in severe COPD. Chest. 2006;**130**(6):1687-1694

[63] Chang SS, Chen S, McAvay GJ, Tinetti ME. Effect of coexisting chronic obstructive pulmonary disease and cognitive impairment on health outcomes in older adults. Journal of the American Geriatrics Society. 2012;**60**:1839-1846

[64] Chen J, Lin IT, Zhang H, et al. Reduced cortical thickness, surface area in patients with chronic obstructive pulmonary disease: A surface-based morphometry and neuropsychological study. Brain Imaging and Behavior. 2016;**10**:464-447

[65] Dodd JW, Getov SV, Jones PW. Cognitive function in COPD. The European Respiratory Journal. 2010;**35**:913-992

[66] Tudorache V, Traila D, Marc M, et al. Impact of moderate to severe obstructive sleep apnea on the cognition in idiopathic pulmonary fibrosis. PLoS One. 2019;**14**(2):e0211455

[67] Pierobon A, Sini Bottelli E, Ranzini L, et al. COPD patients' self-reported adherence, psychosocial factors and mild cognitive impairment in pulmonary rehabilitation. International Journal of Chronic Obstructive Pulmonary Disease. 2017;**12**:2059-2067

[68] Rogliani P, Ora J, Puxeddu E, et al. Adherence to COPD treatment: Myth and reality. Respiratory Medicine. 2017;**129**:117-123

[69] Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: Key concepts and advances in pulmonary rehabilitation. American Journal of Respiratory and Critical Care Medicine. 2013;**188**(8):e13-e64

[70] Chin A, Paw MJM, van Uffelen JGZ, Riphagen I, van Mechelen W. The functional effects of physical exercise training in frail older people. Sports Medicine. 2008;**38**(9):781-793. DOI: 10.2165/00007256-200838090-00006

[71] Palange P, Rohde G, editors. ERS Handbook of Respiratory Medicine. 2019. DOI: 10.1183/9781849840798.erh01. ISBN (electronic): 978-1-84984-079-8

[72] Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. American Journal of Respiratory and Critical Care Medicine. 2011;**183**:431-440

[73] Kreuter M, Ehlers-Tenenbaum S, Palmowski K, et al. Impact of comorbidities on mortality in patients with idiopathic pulmonary fibrosis. PLoS One. 2016;**11**(3):e0151425

[74] Raghu G, Amatto VC, Behr J, et al. Comorbidities in idiopathic pulmonary fibrosis patients: A systematic literature review. European Respiratory Journal. 2015;**46**:1113-1130

[75] Oldham JM, Collard HR. Comorbid conditions in idiopathic pulmonary fibrosis: Recognition and management. Frontiers in Medicine (Lausanne). 2017;**4**:123

[76] Javaheri S, Sicilian L. Lung function, breathing pattern, and gas exchange in interstitial lung disease. Thorax. 1992;**47**:93-97

[77] Findley LJ, Ries AL, Tisi GM, et al. Hypoxemia during apnea in normal subjects: Mechanisms and impact of lung volume. Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology. 1983;**55**:1777-1783

[78] Troy LK, Corte TJ. Sleep disordered breathing in interstitial lung disease: A review. World Journal of Clinical Cases. 2014;**2**:828-834

[79] Pathan SS, Gottesman RF, Mosley TH, et al. Association of lung function with cognitive decline and dementia: The Atherosclerosis Risk in Communities (ARIC) Study. European Journal of Neurology. 2011;**18**:888-898

[80] Lutsey PL, Chen N, Mirabelli MC, et al. Impaired lung function, lung disease and risk of incident dementia. American Journal of Respiratory and Critical Care Medicine. 1 Jun 2019;**199**(11):1385-1396. DOI: 10.1164/rccm.201807-1220OC

[81] Van Dijk EJ, Vermeer SE, de Groot JC, et al. Arterial oxygen saturation, COPD, and cerebral small vessel disease. Journal of Neurology,

Neurosurgery, and Psychiatry. 2004;**75**:733-736

[82] Guo X, Pantoni L, Simoni M, et al. Midlife respiratory function related to white matter lesions and lacunar infarcts in late life. The prospective population study of women in Gothenburg, Sweden. Stroke. 2006;**37**:1658-1662

[83] Yeh H-C, Punjabi NM, Wang N-Y, et al. Vital capacity as a predictor of incident type 2 diabetes: The atherosclerosis risk in communities study. Diabetes Care. 2005;**28**:1472-1479

[84] Schroeder EB, Welch VL, Couper D, et al. Lung functionand incident coronary heart disease: The Atherosclerosis Risk in Communities Study. American Journal of Epidemiology. 2003;**158**:1171-1181

[85] Jiang R, Burke GL, Enright PL, et al. Inflammatory markers and longitudinal lung function decline in the elderly. American Journal of Epidemiology. 2008;**168**:602-610

[86] Schmidt R, Schmidt H, Curb JD, et al. Early inflammation and dementia: A 25-yearfollow-up of the Honolulu-Asia aging study. Annals of Neurology. 2002;**52**:168-174

[87] Sprunger DB, Talbert JL, Brown KK, et al. Cognitive function (CF) is impaired in patients with idiopathic pulmonary fibrosis (IPF). American Journal of Respiratory and Critical Care Medicine. 2009;**179**:A4059. Available from: https://doi.org/10.1164/ajrccm-conference.2009.179.1_MeetingAbstracts.A4059

[88] Sharp C, Adamali H, Millar A, et al. Cognitive function in idiopathic pulmonary fibrosis. Thorax. 2016;**71**:A237

[89] Bors M, Tomic R, Perlman D, et al. Cognitive function in idiopathic pulmonary fibrosis. Chronic Respiratory Disease. 2015;**12**(4):365-372

[90] Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society. 2005;**53**(4):695-699

[91] Perez-Padilla R, West P, Lertzmann M, et al. Breathing during sleep in patients with interstitial lung disease. The American Review of Respiratory Disease. 1985;**132**:224-229. DOI: 10.1164/arrd.1985.132.2.224