Chronic Respiratory Diseases and Neurodegenerative Disorders: A Primer for the Practicing Clinician

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Highlights of the Study

- Neurodegenerative and respiratory diseases are strongly connected by ageing and shared risk factors.
- Alzheimer’s disease is related to chronic obstructive lung disease due to smoking, hypoxaemia, and atherosclerosis.
- Neurodegenerative disorders are often associated with an increased prevalence of sleep-disordered breathing.
- Parkinson and parkinsonisms are more often associated with chronic restrictive respiratory insufficiency.

Keywords

Alzheimer’s disease · Parkinson’s disease · Neurologic diseases · Respiratory diseases

Abstract

Chronic respiratory disorders represent a world epidemic. Their incidence and prevalence in the world population is increasing, and especially among elderly subjects, they are commonly associated with other pathologies, often generating a status of high clinical complexity. Neurology, internal medicine, and pneumology specialists should be aware

of the common background of these disorders in order to treat correctly the patient’s comorbid state and optimize the treatment considering potential overlaps. In this review, we aimed to focus on the relationships between chronic respiratory disorders and chronic neurodegenerative diseases at different levels; we review the shared risk factors and the interactions between disorders, the indications to explore respiratory function in neurodegenerative diseases, pathology-pathology and drug-pathology interactions in patients affected by both chronic neurologic and respiratory diseases.

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Introduction

Both chronic respiratory and neurodegenerative disorders are increasing worldwide, along with the other non-communicable diseases, mainly because of ageing of the population [1]. These diseases are both associated with a decreased quality and a reduced expectancy of life. The main link between these conditions is ageing itself; however, other shared risk factors could increase the strength of this association. In this narrative review, we aimed to identify the shared risk factors, the pathology-pathology and drug-pathology interactions between neurodegenerative disorders and chronic respiratory diseases.

Research Strategy

We searched PubMed/MEDLINE for case reports, reviews, and original research articles in the time frame from January 1, 2000 to February 1, 2020. We used MeSH major terms and considered: “Pulmonary Disease, Chronic Obstructive” [MeSH] or “Lung Diseases, Interstitial” [MeSH] or “Asthma,” [MeSH] or “Lung Neoplasms” [MeSH] in combination with “Tauopathies” [MeSH] or “Alzheimer Disease” [MeSH] or “Parkinson Disease” [MeSH] or “Multiple System Atrophy” [MeSH] or “Supranuclear Palsy, Progressive,” [MeSH] or “Corticobasal Degeneration” [MeSH]. The group of reviewers favoured the inclusion of articles from the past 5 years, although they did not exclude highly cited older reports; the reference lists of articles identified by this search strategy was also reviewed, and the working group selected those references judged to be relevant.

Shared Risk Factors and Interactions between Respiratory Diseases and AD

Cigarette smoking has been associated with cognitive deterioration and represents a risk factor for Alzheimer’s disease (AD) [2]. The risk of developing AD increases proportionally with the time of exposure and it has been hypothesized a role of APOE genotype in the association between cigarette smoking and risk of AD [3]: all the evaluated studies report an increased risk for AD in active smokers, with a dose-dependent effect, and to a lesser extent in ex-smokers [4–6]; in the population of smokers, the highest risk has been observed among carriers of the APOE ϵ 4 allele [7]. The typical neuroanatomic alterations observed among smokers are characterized by a reduction of hippocampal volume, while cognitive impairment is mainly due to a memory and learning deficit [8–10]. Smoking is associated with cognitive deterioration with

several other shared physiopathogenetic mechanisms: for example, chronic cerebrovascular pathology, affecting both large and small vessels and COPD in the subset of chronic hypoxaemic subjects, is associated with cognitive deterioration [11].

The relationship between COPD, hypoxaemia, and cognitive deterioration has been extensively evaluated in different clinical settings; a cognitive deterioration without definite neurodegenerative pathology is present in COPD subjects with a prevalence ranging between 10.4% and 48.5% [12–14]. This association however has been confirmed only in patients with more severe COPD forms after covariate adjustment [15]. Moreover, among COPD patients, some pre-clinical neurodegenerative pathologies, such as non-amnesic mild cognitive impairment are more represented than in general population [16]. A chronic obstruction of lung function in younger ages, as in COPD or in asthma, has been associated with a higher risk of mild cognitive impairment or dementia in the geriatric age [17].

AD is also associated with a higher prevalence of sleep-disordered breathing (SDB), particularly OSAS [18, 19]. The association between AD and OSAS is secondary to both central and peripheral alterations and associated with a greater cognitive deterioration in respect to AD alone [20, 21]. In the last years, several authors found that OSAS could be considered a risk factor for progression of cognitive impairment [22, 23].

Moreover, in this subgroup of patients, the cognitive deterioration could be slowed by CPAP treatment [24]. Cancer incidence [25], particularly lung cancer [26], seems to be lower in AD and in other central neurodegenerative diseases. Several observations from animal models, transcriptomic meta-analyses, and matrix factorization studies underline the existence of molecular substrates supporting the hypothesis of an inverse comorbidity relationship between AD and lung cancer [27–29].

Shared Risk Factors and Interactions between Respiratory Diseases and PD

The role of cigarette smoking in Parkinson’s disease (PD) has been extensively studied. Recent meta-analyses underlined a reduced risk of developing PD in previous smokers, which is further reduced in active smokers at the time of the study [30, 31]. The biological rationale of this association is not known, but it is attributed to the effect of nicotine in stimulating dopamine release and modulating the central monoamino-oxydase activity. However, several authors postulated that, despite the high number of articles suggesting this hypothesis, this observation

could be caused by some methodological biases, suggesting that the observed neuroprotective effect of smoking could be associated with reverse causality [32]. Moreover, some retrospective studies underlined a higher risk of PD among COPD patients [33].

Aspiration pneumonia represents the 70% of PD-associated deaths [34]. This pathology should be always suspected in PD patients developing fever or respiratory symptoms, particularly in those with known dysphagia or sialorrhoea; a normal deglutition requires an appropriate pharyngeal and laryngeal stimulation, an adequate muscular tone, and proper coordination between deglutition and action of respiratory muscles. If the bolus is accidentally sent in the airways, cough acts as a protective mechanism. With disease progression, mastication and deglutition are difficult due to bradykinesia, stiffness, and dyskinesias. A sensitive deficit in the glossopharyngeal and vagus nerve territories can contribute to dysphagia [35]. Disturbances in deglutition that increase oral material and accidental aspiration are present in 60% of PD-affected patients. This is important, as aspiration of saliva itself can be a cause of pneumonia, with no relationship with meals. The coordination of breathing with deglutition is dysfunctional in these subjects, and cough becomes less effective for increased chest wall stiffness and a reduction of the sensorial component of cough reflex. The PD medical treatment can improve respiratory function, but levodopa does not seem to improve dysphagia. Sialorrhoea can be treated with anticholinergic drugs, as clonidine, or with surgical resection of salivary glands, radiotherapy, or local treatment with botulinic toxin. Tracheostomy can be suggested as the last preventive measure, to be considered only after an extensive evaluation of the patient and his quality of life. Oropharyngeal dysphagia affects 4 out of 5 PD patients, and it is an often underestimated complication by both patients and caregivers [36]. This symptom, characterized by the chronic aspiration of oral or gastric material due to alterations of deglutition mechanisms, can cause anatomic alterations that can manifest with nodular, multilobular, or centrilobular alterations, “tree-in-bud” and interstitial thickening which can evolve to lung fibrosis [37]. The most common histopathological finding in chronic aspirative pneumonia is compatible with bronchiolitis obliterans-organizing pneumonia, often combined with suppurative granulomas, bronchiolitis, and bronco-pneumopathy associated with suppurative granulomas [38].

The prevalence of restrictive diseases in patients affected by PD varies between 28% and 85% [36], with extreme variability caused by antiparkinsonian drug use.

Dyspnoea associated with restrictive diseases usually starts as an exertional dyspnoea which progressively evolves into a resting dyspnoea associated with a worsening of typical PD motor symptoms, such as falls or gait freezing [39]. The pathophysiological mechanisms underlying this are not well understood. The pathophysiological mechanisms of restrictive breathing disorders have still not been completely elucidated, albeit mainly associated with stiffness and bradykinesias of respiratory muscles and to reduced compliance of the thoracic wall. Spirometry is compatible with muscle weakness of thoracic wall muscle weakness which is similar to peripheral neuromuscular disease, but there is little evidence of this effect in PD [40]. Osteomuscular alterations of the neck, as camptocormia, can contribute to restrictive pattern, thus limiting thorax expansion and reducing respiratory volumes [41–43]. A restrictive respiratory insufficiency in the setting of PD usually improves with dopaminergic treatment, which could be less effective in the most advanced stages of disease [42]. In the subset of patients in whom camptocormia is present, respiratory exercises can be effective, but this indication comes from a single case report [44]. A vigorous program of respiratory rehabilitation seems to be able to improve both respiratory and cardiovascular function [45, 46].

In the last decade, several authors underlined a very high prevalence (43–66%) of SDB in PD [47–50]. Several studies suggested that a central component, associated with neurodegeneration, and a peripheral component, associated with upper respiratory muscles atonia, can be at the origin of SDB in PD [51]. In PD, OSAS is not necessarily related to obesity and can be associated with an increased diurnal sleepiness [52, 53]. Several studies and meta-analyses underlined that, excluding malignant melanoma; other forms of cancer are usually under-represented in PD, especially lung or smoke-related tumours [54–56].

Shared Risk Factors and Interactions between Respiratory Diseases and PSP

There are no studies evaluating the association between progressive supranuclear palsy and COPD, lung cancer or interstitial lung disease, and further research is required in this direction. However, early dysphagia and pneumonia have been associated with increased mortality [57].

Shared Risk Factors and Interactions between Respiratory Diseases and Parkinsonisms (MSA, CBD)

There are no studies evaluating the association between multisystem atrophy (MSA) or corticobasal degen-

eration and COPD, lung cancer, or interstitial lung disease. Parkinsonisms however can often show several forms of dystonia involving the upper airways (vocal cords and larynx) or diaphragm motility [58]. This aspect, when associated with the common reduction of cough reflex and oropharyngeal dyssynergy, represents a risk factor for several types of respiratory comorbidities, from aspiration pneumonia to acute respiratory insufficiency. MSA is associated with a greater incidence of SDB, particularly OSAS and stridor. Daytime or nocturnal stridor is present up to 50% of the patients, and is more frequent in the advanced stages of the disease [59]. OSAS can affect 40% of MSA patients and can be associated with stridor [60]. The pathophysiological mechanism of stridor can be attributed to the dystonic contraction of the adductor muscles of larynx during inspiration, which can lead to an active constriction of larynx [61]. This non-motor manifestation is associated with reduced survival and with an increased risk of sudden death in AMS [62] but can be treated with nocturnal CPAP or invasive ventilation [63, 64].

Exploring Respiratory Function and Structure in AD

Spirometric alterations in the midlife were associated with a greater risk of AD [65] but also with an increase in white matter lesions and lacunar infarcts, which are associated with vascular dementia [66]. Ventilatory alterations later in the life, evaluated with spirometric indices (PEF-R, FEV1, MEF50% FVC, and MEF25% FVC), have been associated with a greater risk of dementia independently from other known risk factors for AD [67]. A reduced lung function and the presence of a restrictive pattern in younger ages have been associated with a greater risk of dementia in advanced age [67].

Exploring Respiratory Function and Structure in PD and Parkinsonisms

Respiratory involvement in PD or parkinsonisms can be categorized as upper airways obstruction, restrictive pattern, complications secondary to drug withdrawal or use, and aspiration pneumonia. The difference between PD and parkinsonisms in term of respiratory function involvement is slight but significant. MSA, PSP, and PD share the same low central response to hypoxia, a high risk of aspiration pneumonia, and a high prevalence of SDB. PD however has a broader respiratory involvement comprising also restrictive pathology, SDB, diaphragmatic dyskinesias, and aspiration pneumonia. Upper airways obstruction is common in all the 3 forms, but it is more marked in PD due to multiple mechanisms of dis-

ease, while the upper airways in MSA and PSP are often obstructed by mechanisms of laryngeal stridor.

Effect of Drugs Adopted in Neurodegenerative Diseases in Respiratory Function in AD

Donepezil, galantamine, and rivastigmine are commonly used for the treatment of AD and act as cholinesterase inhibitors. Thus, their use, albeit not contraindicated, can be associated with exacerbation of COPD and must be strictly controlled [68], while bronchial asthma represents an absolute contraindication to their use. The use of these drugs is associated with nausea and vomiting in a percentage between 5 and 31% in various trials. There is only 1 case report which correlates this effect to aspiration pneumonia [69]. Donepezil however seems to have an effect in reducing the entity of SDB [70].

Effect of Drugs Adopted in Neurodegenerative Diseases in Respiratory Function in PD and Parkinsonism

Long-term complications of levodopa treatment include involuntary movements typically involving head, trunk, and limbs. A “respiratory dyskinesia” can represent the manifestation of a motor complication related to levodopa. Choreic, stereotyped and dystonic movements are present in the long-term treatment with levodopa and can interfere with a regular respiratory pattern generating dyspnoea, tachypnoea, or an irregular respiratory pattern. Moreover, levodopa can induce an oromandibular or laryngeal dystonia [71, 72] which can generate a worsening of respiratory disease by obstructing the upper airways. These respiratory disorders tend to resolve with the drug suspension, but in some cases levodopa withdrawal has been associated with a worsening of larynx dystonia, stridor, and chest muscular stiffness, which can be further worsened by panic crises induced by the reduced capacity of expanding the chest [73–75].

The mechanisms of levodopa-induced respiratory dyskinesia are not well understood; however, it has been hypothesized a hypersensitivity due to a denervation of dopaminergic receptors mediated by exogenous dopamine in central chemoreceptors [76]. Dopamine is adopted both in central pontine and peripheral chemoreceptors. As hypoxia increases, endogenous dopamine synthesis and release from carotid receptor cells increase [77]. A reduced peripheral chemosensitivity could, at least in part, justify the reduced response to hypoxaemia observed in PD [78]. This complication should be treated as the other levodopa-associated motor fluctuations and dyskinesias [79]. Some case-reports underlined that cab-

ergoline, pergolide, bromocriptine, and ergot-derived drugs can be associated with lung and pleural fibrosis and with pleural effusions. Symptoms can be severe, being not observed in patients not assuming other dopamine agonist agents, as pramipexole or rotigotine [80–82]. Respiratory symptoms typically appear within 3 years from treatment start; however, some cases are described up to 11 years from the beginning of treatment [83]; these subjects develop a dyspnoea associated with an interstitial lung disease associated with pleural effusion or pleural thickening, with a restrictive spirometric pattern. Histopathology underlines lung and pleural fibrosis, with chronic inflammatory infiltrate [83]. The mechanism of disease is not well-understood, and some authors suggest that ergot agonists can activate the lung 5HT-2B receptors and stimulate fibroblasts, inducing cell growth, growth factors production, and extracellular matrix production [84].

Effect of Drugs Adopted in Respiratory Diseases in AD

Inhaled anticholinergic drugs use has been associated with a greater risk of cognitive deterioration [85, 86], and among elderly patients, to more hospital admissions for delirium [87]. Inhaled steroids use has been associated with an increased risk of cognitive deterioration among female individuals [88]. Treatment for lung cancer has been associated with a deterioration of verbal and visuospatial abilities, and associated with anatomic alterations in limbic regions and in white and grey matter of the cortex [89].

Effects of Drugs Used in Respiratory Diseases in PD and Parkinsonisms

Some studies underlined a positive effect of long-acting beta-2 agonists as salmeterol in reducing Parkinson and parkinsonisms symptoms in the animal model [90,

91], but there are no studies confirming a positive effect of this class of inhalator drugs used in COPD in this group of degenerative diseases. Inhaled anticholinergic drugs, as tiotropium or ipratropium bromide have a potential synergistic effect with antiparkinsonian drugs, as levodopa. This can increase the therapeutic effect of levodopa but also increase the collateral effects, as late dyskinesia. Ipratropium bromide, in inhaled formulation, has also been suggested as a potential treatment for sialorrhoea in patients affected by PD and parkinsonisms [92, 93].

Conclusions

As clinical complexity increases, mainly due to ageing of the population, different professionals must be aware of the common risk factors and of the potential interactions between chronic respiratory disorders and neurodegenerative diseases.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

L.F., G.V.: conceptualization, methodology, investigation (review) and writing (original draft); V.Z., N.T., L.N., C.N.: investigation (review), writing (review and editing) and data curation; A.S., G.M., M.S.: conceptualization, validation, supervision and writing (review and editing).

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