REVIEW
PARKINSON'S DISEASE

Respiratory dysfunction in Parkinson's disease: a narrative review

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ABSTRACT The presence of respiratory symptoms in Parkinson's disease (PD) has been known since the first description of the disease, even though the prevalence and incidence of these disturbances are not well defined. Several causes have been reported, comprising obstructive and restrictive pulmonary disease and changes in the central ventilatory control, and different pathogenetic mechanisms have been postulated accordingly. In our review, we encompass the current knowledge about respiratory abnormalities in PD, as well as the impact of anti-Parkinsonian drugs as either risk or protective factors. A description of putative pathogenetic mechanisms is also provided, and possible treatments are discussed, focusing on the importance of recognising and treating respiratory symptoms as a key manifestation of the disease itself. A brief description of respiratory dysfunctions in atypical Parkinsonism, especially α-synucleinopathies, is also provided.

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This review addresses current knowledge about respiratory dysfunctions in Parkinson's disease, from the aetiopathology to pharmacological and invasive treatments, describing the different clinical phenotypes https://bit.ly/2X7OLtN

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Introduction

Parkinson's disease (PD) is a neurodegenerative disorder due to a progressive loss of striatal dopamine, thus leading to tremor, bradykinesia, rigidity and postural instability.

The presence of respiratory abnormalities in PD has been well known for many years, but its prevalence is probably underestimated. In his first description, PARKINSON [1] noted this association describing a man who "fetched his breath rather hard". Since the half of the last century, many studies have discussed respiratory impairment in PD, even in early stages and in asymptomatic patients [2]. Respiratory dysfunctions may be responsible for the mortality and morbidity associated with PD [3]. Although respiratory changes are usually correlated with peripheral motor impairment [4–6], several causes have been reported, including obstructive and restrictive patterns, as well as changes in the central ventilatory control. Overall, respiratory dysfunctions in PD seem to correlate with motor scores, but the relationship with pharmacological therapies, disease phenotypes and nonmotor symptoms is not completely understood.

In this review, we encompass the current knowledge about respiratory changes in PD, focusing on obstructive and restrictive patterns, as well as on the role of the central respiratory control, highlighting the underlying putative pathogenetic mechanisms. A brief discussion about pneumonia in PD it is also provided; an overview of the impact of anti-Parkinsonian drugs and deep brain stimulation (DBS) is also described. Finally, we briefly discuss the presence of respiratory abnormalities in atypical Parkinsonisms, especially multiple system atrophy (MSA), dementia with Lewy bodies (DLB) and supranuclear palsy (PSP).

Materials and methods

A literature search was updated from March 2019 to June 2020 and referred to PubMed and Google Scholar, using the terms "Parkinson's disease", "Parkinson", "Parkinson disease" combined with "respiratory failure", "drugs respiratory failure", "pulmonary dysfunction", "respiratory dysfunction" and "ventilatory dysfunction". Another search combined the terms "Parkinson's disease", "Parkinson", "Parkinson disease" with terms "sleep" and "sleep apnea". We included articles in English only. Exclusion criteria included animal studies and other neurological disorders different from PD or Parkinsonisms.

Obstructive respiratory dysfunction

Several studies have shown obstructive respiratory dysfunction in PD (table 1). Many authors have described upper airway obstruction (UAO), with a highly variable prevalence ranging from 6.7% to 67% [8, 9]. Dyspnoea could be a manifestation of UAO, even if other common indicators may include hypophonia, shaky voice, stridor or wheeze [17].

Two types of UAO have been described by spirometry and fibre optic endoscopy for the first time by VINCKEN and co-workers [7], and was further confirmed by subsequent studies [8, 9, 11]. The first type ("respiratory flutter") is characterised by regular consecutive flow decelerations and accelerations superimposed on the general flow-volume loop, with a frequency similar to the hands' tremor (5–8 Hz). In the second type, abrupt and irregular changes in flow (often dropping to zero) are seen on an abnormal flow-volume loop due to irregular and jerky movements of the glottic and supraglottic structures, thus leading to intermittent airways closure.

Although the pathophysiology is still debated, both patterns probably reflect dysfunctions in the basal ganglia (figure 1). In PD, α-synuclein deposition starts in the caudal portion of the brainstem, involving the dopaminergic neurons in the substantia nigra (SN) [18]. Loss of dopaminergic stimulation is known to lead to motor disturbances such as tremor, bradykinesia and rigidity and movement abnormalities in the phonatory structures may ultimately resemble those observed in peripheral muscles. These data are consistent with electromyographic abnormalities of laryngeal, rib cage and neck muscles [19, 20], even if these changes are not specific and may be present also in other movement disorders [7].

A possible correlation between UAO and tremor has been reported by some authors [21], even if it should be stated that other types of Parkinsonisms were included in the study. SABATÈ *et al.* [9] have, nevertheless, reported the association of UAO with bradykinesia more than rigidity and tremor. Moreover, an association of UAO with dystonia has been described by JANKOVICH *et al.* [22]. All these data seem to further suggest a correlation between UAO and peripheral motor disorders, due to basal ganglia dysfunctions. UAO has been correlated also with dorsal column arthrosis, which may be explained by chronic anomalous postures in advanced stages [9].

Lower airway obstruction has been reported and differentiated by UAO in the work of SABATÈ *et al.* [9], correlating with rigidity, resistance to passive mobilisation of the cervical column and cervical spine arthrosis. Obstructive abnormalities have been described in other papers, although differences between UAO and lower airway obstruction have not been systematically assessed [14–16]. Moreover, a small

TABLE 1 Main studies considered in our review about the presence of obstructive, restrictive and central respiratory dysfunction in Parkinson's disease patients

First author [ref] (year)	Number of patients	Clinical score	Disease duration	Pharmacological washout	Obstructive defect	Restrictive defect	Central ventilatory dysfunction
Vincken [7] (1984)	27	H&Y 4 (mean in the obstructive patients)	Not available	Not reported	10 (upper airway)	Not found	Not assessed
Izquierdo-Alonso [8] (1994)	63	H&Y 2.55 (mean), UPDRS 30 (mean)	5 years (mean)	No	13 (upper airway)	54	Not assessed
Sabatè [9] (1996)	58	UPDRS III, mean not available	Not available	8 h	36 (upper airway) *versus* 21 (lower airway)	16	Not assessed
Onodera [10] (2000)	25	H&Y 2–3	Not available	No	Not assessed	Not assessed	Impairment response to hypoxia *versus* control group
Herer [11] (2001)	21	H&Y 2.6 (mean)	0.25–11 years	12 h	5 (upper airways obstruction)	Not found	Not assessed
De Pandis [12] (2002)	12	H&Y 4.08 (mean)	8–25 years	12 h	Not found	More severe pattern in off stage	Not assessed
Weiner [13] (2002)	20	H&Y 2–3, UPDRS III 41.4 (mean in off)	Not available	Not reported	Not found	Mild restrictive pattern	Not assessed
Sathyaprabha [14] (2005)	35	H&Y 1–2	1–5 years	12 h	2	33	Not assessed
Seccombe [15] (2011)	19	H&Y 2.5 (mean)	2–23 years	No	1	2	Impairment response to hypercapnia *versus* control group
Baille [16] (2018)	41	UPDRS III 19 (mean)	0.20–3.6 years	12 h	6	1	Not assessed

H&Y: Hoehn & Yahr; UPDRS: Unified Parkinson's Disease Rating Scale.

number of obstructive pattern patients in PD was found in these studies, and no further characterisation has been provided to date [14–16].

Differences among studies may be related to the characteristic of the cohorts examined such as number of the patients enrolled, disease duration and the timing of pharmacological washout before the spirometric evaluation (table 1).

Restrictive respiratory dysfunction

Papers describing a restrictive respiratory pattern are summarised in table 1. Restrictive respiratory dysfunction has been described both in symptomatic and asymptomatic patients, with variable prevalence ranging from 28% to 94% [8, 9, 12, 14].

Even for restrictive dysfunction, the pathogenesis is controversial; several hypotheses have been postulated, including dysautonomia related to PD and adverse effects referred to ergot-derived drugs [8, 9], whereas myopathic weakness of the chest wall seems unlikely (figure 1) [5, 23]. No correlation with tremor, bradykinesia or rigidity has been described, while a probable relationship with dorsal spine arthrosis has been postulated [9]. Moreover, some authors reported a correlation with motor features, such as gait freezing and falls, in moderate to severe PD, and a correlation with camptocormia and kyphoscoliosis in more advanced stages [24].

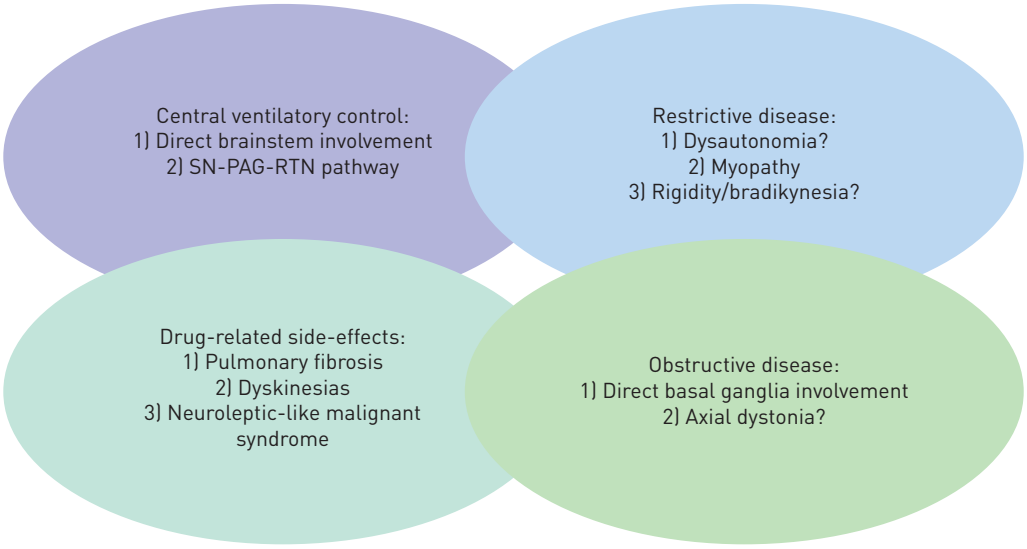

FIGURE 1 Putative contributing mechanisms leading to respiratory dysfunctions in Parkinson's disease and atypical Parkinsonisms. SN: substantia nigra; RTN: retrotrapezoid nucleus; PAG: periaqueductal grey.

Others reported conflicting data showing a possible correlation with rigidity and bradykinesia, but not with tremor [25]. These data may be, at least in part, in line with other studies. De Pandis *et al.* [12] identified a restrictive pattern in a cohort of advanced parkinsonian patients (mean Hoehn and Yahr stage 4.08) worsened in the "off" condition, probably due to chest wall muscle rigidity and reduction of chest wall range of movements. Similar results were obtained by Sathyaprabha *et al.* [14], showing a high percentage of PD patients with a restrictive pattern worsened during the "off" condition and more pronounced in later stages (Hoehn and Yahr 2).

Even in this case, reduction in rigidity may result in improved muscle coordination and facilitation of chest wall movements. A really small number of restrictive pattern patients was found in other studies, but these patterns have not been further characterised (table 1) [15, 16].

Central ventilatory control

As aforementioned, the deposition of α-synuclein in PD starts in the caudal portion of the brainstem, and structures involved in the respiratory control, as those responsible for coordinating ventilation and detecting peripheral hypoxaemia or hypercapnia, may be directly affected by neurodegeneration at an early stage [18, 26–29].

These data seem to agree with what has been reported in literature. Onodera *et al.* [10] described a reduced central chemosensitivity to hypoxia even in the early stages, without abnormalities in the response to hypercapnia. Other authors, as opposed, found an abnormal ventilatory response to carbon dioxide in patients with normal lung volumes and flows, especially in mild to moderate PD, but not for mild hypoxia (table 1) [15].

Despite these little discrepancies among different studies, according to the Braak hypothesis, the early involvement of the brainstem in PD may lead to dysfunction of the medullary respiratory centres and consequently of the central drive of breathing [30]. Moreover, other mechanisms have been reported to explain the impaired central control (figure 1). Neurodegeneration involves not only dopaminergic neurons, but also astrocytes: losing astrocytes in key regions involved in breathing activity will produce ATP deficiency, which in turn will fail to stimulate breathing [31–33].

In addition, an indirect mechanism underlying central ventilator control has been recently proposed in animals, basing on the demonstration of a di-synaptic excitatory pathway from the dopaminergic neurons of the SN to the retrotrapezoid nucleus (RTN), passing through the periaqueductal grey (PAG) [34]. PAG is engaged in a number of physiological functions, comprising nociception, arterial pressure and heart rate, while RTN is critically involved in the chemosensory control of breathing [31, 35–37]. PAG also coordinates motor output, including respiratory muscles, based on the integration of input arising from limbic, pre-frontal and anterior cingulate cortex regions [38]. Overall, degeneration of SN dopaminergic neurons, as occurs in PD, may lead to a progressive loss of functions along the SN–PAG–RTN pathway. These findings further emphasise the key role of a central breathing control failure in PD respiratory

dysfunction, in addition to the loss of dopaminergic stimulation due to the direct basal ganglia involvement.

Central breathing dysfunction may explain at least in part the abnormal perception of dyspnoea (POD), as reported in some papers. Many patients with spirometric abnormalities may be asymptomatic, and blunted POD may contribute. The reduced response to hypoxia described by Onodera *et al.* [10] may play an important role. This report, however, is not consistent with a more recent study, which demonstrated an increased POD in PD compared to controls [13]. Physiologically, dyspnoea is perceived as respiratory muscle effort, and the degree of perception is linked to the strength of respiratory muscles [39]. The patients examined by Weiner *et al.* [40] had an abnormal pulmonary test function (restrictive pattern and inspiratory muscle endurance) and a more severe disease compared to the cohort of Onodera *et al.* [10] so in this case mechanical factors may have contributed to the increased POD.

Mechanical factors, independently or in addition to a central dysfunction, may also explain the exacerbated POD in patients experiencing respiratory dyskinesias [40].

Apnoea in Parkinson's disease

The presence of apnoea syndrome has been studied in PD as well. Apnoea syndrome is probably related to a central dysfunction of the brainstem respiratory centres and/or a peripheral airways involvement. However, different studies have produced conflicting results, probably according to the different samples of patients and methods used.

Apnoea occurring during sleep could be classified as central (if the airflow drops down due to a failure in activation of respiratory muscles), obstructive (if the occlusion of the upper airways stops the airflow despite respiratory muscle effort) and mixed [41]; nonetheless, these patterns have not been studied systematically in PD and a clear stratification is not available in the current literature. Most studies focused on obstructive apnoea rather than central.

Conflicting results have been reported about the prevalence of obstructive apnoea syndrome in PD patients; Maria *et al.* [42] identified a higher prevalence of obstructive apnoea in PD populations, whereas others found less occurrence of obstructive apnoea compared to controls [43, 44], or even no apnoea or sleep abnormalities [45]. De Cock *et al.* [44] tried to explain this phenomenon, postulating a possible protective contribution due to rapid eye movement (REM) sleep behaviour disorder (RBD), in which the physiological muscle atonia during REM sleep is absent and may prevent upper airway closure.

Surprisingly, the authors found that patients with abnormal persistence of chin muscle tone still presented obstructive apnoea during REM sleep, and similar findings were described by Huang *et al.* [46]. It may be reasonable that there is a correlation between motor disability and apnoea, as suggested in some studies [42, 44], but the role of PD medications is not clear, and it has to be specified that in these studies, motor disability and apnoea were assessed in the "on" state, so the real contribution of dopaminergic drugs could not be clearly assessed. Continuous positive airway pressure (CPAP) seems to be effective in reducing events, improving oxygen saturation, and deepening sleep in patients with PD and obstructive sleep apnoea [47, 48].

The issue of pneumonia in Parkinson's disease

Aspiration pneumonia represents a dramatic complication that may explain the acute/subacute onset of fever and respiratory insufficiency in a PD patient. Physiologically, swallowing requires adequate coordination between pharyngeal and respiratory musculature, but this mechanism is frequently impaired in PD [49]. Dysphagia is typical in the advanced stages of disease, on average 10–11 years after motor symptoms onset [50], when bradykinesia, rigidity and dyskinesias are predominant; however, a cough dysfunction in more than 50% of asymptomatic PD patients has been demonstrated [51] and this may also contribute to silent aspiration and increased risk of pneumonia [52]. Moreover, in these patients the cough mechanism becomes weak because of cough reflex impairment and chest wall rigidity, further increasing the risk of aspiration [53]. A blunted urge to cough (UTC), a respiratory sensation that precedes the cough reflex, is also present and correlates with the severity of dysphagia and consequently, with an increased risk of aspiration [54].

The key for adequate management of aspiration pneumonia is prevention. A soft mechanical diet is usually the first step, followed as dysphagia progresses, by liquid thickening. A chin-down posture while swallowing may be helpful, and sometimes a speech or swallowing therapist may be required. The beneficial role of dopaminergic stimulation is controversial; despite the importance of dopaminergic basal ganglia circuits in the swallowing process [55], conflicting results have been reported by different studies [56, 57]. Finally, for patients with marked sialorrhea, who may have an increased risk of aspiration, treatment with anticholinergics drugs or botulinum injections in the salivary glands may be indicated.

Effects of dopaminergic therapy: risk or protection?

Studies have provided controversial results about the therapeutic effects of dopaminergic stimulation, and the role of drugs commonly used in the treatment of PD is still debated, strictly depending both on disease stage and administration modality.

Most papers strengthen the role of anti-Parkinsonian drugs as a protective factor against the development of respiratory failure. Levodopa increases inspiratory muscle function in anaesthetised dogs [58], and dopamine improves diaphragm function during acute respiratory failure in patients with COPD [59]. In early stages, the levodopa equivalent daily dose does not correlate with pulmonary functional testing; as the disease progresses, anti-Parkinsonian medications may be responsible for the maintenance of the maximal inspiratory mouth pressure and sniff nasal inspiratory pressure [16]. Accordingly, bedtime controlled-release levodopa (Sinemet CR) is associated with less severe obstructive sleep apnoea in PD [60]. Because dopamine is not known to increase muscle strength, it may ameliorate respiratory function by improving muscle coordination by a central activity [16].

Among the side effects of anti-Parkinsonian drugs, we have to consider pleura-pulmonary fibrosis induced by dopamine agonists like bromocriptine [61], and levodopa-induced diaphragmatic dyskinesias, which may present as marked dyspnoea [40, 62, 63]. The presence of other dyskinesias more commonly seen in PD, such as trunk, face or limb abnormal involuntary movements, should alert the physician to the presence of diaphragmatic dyskinesias in patients complaining of breath shortness.

Many authors have investigated the effect of dopaminergic therapy on aforementioned respiratory dysfunction, especially on obstructive and restrictive patterns (table 2).

Indirect evidence of the beneficial role of dopaminergic therapy on the UAO has been supported by the acute respiratory failure that may occur after these medications are suspended [65, 66], or by the response of UAO to intravenous apomorphine [67, 68]. Further evidence about the beneficial effect of dopaminergic therapy on UAO was provided by Herer *et al.* [11]. In contrast, other authors strengthened a key role of dopaminergic drugs in reversing, at least partially, restrictive changes [12, 14, 25, 64]. However, a recent meta-analysis of four major clinical trials showed no clear effects of dopaminergic stimulations on the obstructive pattern [11, 12, 14, 64], proving some efficacy on restrictive pattern parameters instead [69]. In this view, there are only few data about the effects of dopaminergic agents on brainstem ventilatory control. Interestingly, Weiner *et al.* [13] demonstrated an attenuated POD after levodopa intake; given that the respiratory muscle strength was not significantly different in the "on" compared to the "off" condition, the authors speculated about a possible central effect of levodopa contributing to the decrease of POD.

These discrepancies may be explained at least in part by the different study design and the different characteristics of the cohort such as number of patients, PD duration and severity; differences in the dosage of levodopa administered in the "off" stage and in the duration of pharmacological washout may also play a role. Only one of those studies is considered to have specified a different washout timing for levodopa and dopamine agonist [25], and only one has assessed spirometry after a standardised weight-based levodopa intake [11].

Finally, a growing body of evidence suggests that both a sudden withdrawal and a significant reduction of anti-Parkinsonian drugs are risk factors for the so-called neuroleptic malignant-like syndrome (NMLS), a rare but severe clinical condition, resembling the well-known neuroleptic malignant syndrome, characterised by hyperthermia, impaired consciousness, autonomic dysfunction (*e.g.* respiratory failure) and elevated serum creatine kinase levels. Independent risk factors for NMLS are the use of cholinesterase inhibitors, a rapid switchover from bromocriptine to pergolide and enteral nutrition, as high protein intake critically impairs the absorption of levodopa [70–72].

Finally, only few data have been reported concerning the relationship between the enteral infusion of levodopa and the development of respiratory dysfunctions, except for sporadic cases of pneumonia and pulmonary embolism [73].

Correlation between pneumological drugs and PD

In this scenario, the effects of drugs commonly used by the pneumologist should also be considered. For instance, some studies recently reviewed by Hopfner *et al.* [74] postulated the possible correlation between β-adrenoreceptors (both agonists and antagonists) and PD [75]. Anticholinergic drugs are frequently used for obstructive pulmonary disorders and systemic anticholinergics may play a part in PD [76]. Acetylcholine has a key role in modulating dopaminergic activity in the basal ganglia, and its inhibition may increase central dopaminergic tone [77]. Anticholinergic bronchodilators might have central effects, as reported by some authors [78]. An effect on motor disturbances in PD may be reasonable, even if to our knowledge this has not been investigated in the current literature. However, it

TABLE 2 Main findings of major studies we considered about the effects of dopaminergic drugs on respiratory parameters and respiratory dysfunctions

First author [ref] (year)	Number of patients	Clinical score	Disease duration	Pharmacological washout	Study design	Main results
Herer [11] (2001)	21	H&Y 2.6 (mean)	0.25–11 years	12 h	PD patients *versus* control group. Basal spirometry (pharmacological washout) then spirometry after 45–60 min of levodopa administration (1–2.6 mg·kg^{-1}) *versus* placebo	Improvement of obstructive parameters and/or of saw-tooth spirometry pattern after levodopa
De Pandis [12] (2002)	12	H&Y 4.08 (mean)	8–25 years	12 h	PD patients with fluctuating symptoms; spirometry in on state *versus* off state	Restrictive pattern in severe PD, with worsening in the off state
Weiner [13] (2002)	20	H&Y 2–3, UPDRS III 41.4 (mean in off)	Not available	Not reported	Spirometry in on *versus* off state compared to healthy controls	Mild restrictive pattern not influenced by levodopa; decreased respiratory muscle strength and endurance in off state, with a nonsignificant trend to increase after levodopa. POD attenuated after dopaminergic medications
Sathyaprabha [14] (2005)	35	H&Y 1–2	1–5 years	12 h	PD patients *versus* control group. Spirometry in off state *versus* on state	Predominantly restrictive pattern ameliorating with levodopa (on condition)
Lim [64] (2008)	10	H&Y 2.4 (mean)	8.5 years (mean)	12 h	PD patients, spirometry in on condition *versus* off condition	Improvement of restrictive parameters in on condition, even if small
Pal [25] (2007)	53	H&Y 2.4 (mean)	3.1 years (mean)	12 h for levodopa, 18 h for dopamine agonists	PD patients *versus* controls; spirometry in off condition after washout *versus* on condition	Restrictive disfunction partially reversed by levodopa
Baille [16] (2018)	41	UPDRS III 19 (mean)	0.20–3.6 years	12 h	Spirometry at the time of recruitment and then two after 2 years of follow-up (both on pharmacological washout)	Inspiratory muscle weakness at time of recruitment, without worsening after 2 years. Motor outcome not different among PD patients with inspiratory muscle weakness compared to patients without

PD: Parkinson's disease; H&Y: Hoehn & Yahr; UPDRS: Unified Parkinson's Disease Rating Scale; POD: perception of dyspnoea.

should be considered that anticholinergics may be associated with cognitive impairment and delirium [78], and these adverse effects may be even more common in the advanced stage of PD, when dementia is a very common feature.

Deep brain stimulation and respiratory failure

DBS is an effective strategy for the treatment of advanced PD, thus improving motor fluctuations and bradykinesia.

Nonetheless, the classical target of the subthalamic nucleus (STN)-DBS reserves stimulation-induced side effects in the long-term period, comprising gait and speech impairment, as well as a progressively worsening of tremor. In this scenario, only few papers have specifically investigated respiratory failure. In particular, STN-DBS may increase the risk of a fixed epiglottis and modify velopharyngeal control [79]; these effects seem to strictly depend on frequency parameters, with low-frequency stimulation leading to a

clinical improvement, whereas higher frequencies are associated with a detrimental effect on velopharyngeal control [80].

In support of this view, Hammer *et al.* [81] have recently found that in STN-DBS patients, respiratory changes do not correlate with limb function, but speech-related respiratory and laryngeal control may benefit when the stimulation is delivered at low frequencies (145 Hz) and shorter pulse width (60 µs). In addition to stimulation frequency, other factors may account for these correlations, including variability in localisation of the active DBS electrodes, individual variability in somatotopic organisation of STN, stimulation fields and potential current spread beyond the STN target (*e.g.* internal capsule). Data on the relationship between respiratory changes and novel DBS targets, such as the pedunculopontine nucleus (PPN), have not been extensively reported so far.

PPN has been only recently suggested as a new target for DBS in PD, given its key role in gait control and posture maintenance [82].

PPN surgery may modify central ventilation control, as PPN directly changes sympathetic activity [83]; moreover, PPN could indirectly modulate both breathing regulation, through cholinergic projections to RTN, and expiratory output arising from the parafacial respiratory group in the ventrolateral medulla [84].

A recent study has confirmed beneficial effects of low-frequency PPN-DBS on the upper airways function, also showing a significant correlation between the increase of oscillatory α-band activity and forced respiratory manoeuvres [85]; this effect was particularly marked when the rostral PPN was stimulated, as a part of the "mesencephalic locomotor region" (MLR); in animal studies, the MLR has been shown to project directly to a medullary respiratory generator and plays a key role in changes in respiration linked to motion [86].

Respiratory dysfunction in Parkinsonisms

As described above, the presence of respiratory dysfunction in PD may be explained, at least in part, by dysregulation in basal ganglia and in other brainstem structures that control the central respiratory drive or peripheral airway muscles. In this scenario, it is reasonable to assume the presence of some kind of dysfunction in other forms of Parkinsonism, either secondary or primary degenerative, in which these structures may be involved [22, 87].

Besides this, to the best of our knowledge, systematic studies on degenerative parkinsonians are still lacking, with only few data currently available about MSA and DLB, two degenerative disorders belonging to α-synucleinopathies along with PD.

Respiratory dysfunction is considered one of the "red flags" that may help to distinguish PD from MSA [88], and includes nocturnal stridor and obstructive sleep apnoea [89]. In MSA, deposition of synuclein preferentially involves the caudal brainstem and the ventral medullary region, a key area for the vocal cord control and central respiratory drive [90]. Respiratory dysfunction, including sleep disordered breathing as inspiratory stridor, represents a typical feature of MSA and probably reflects degeneration of brainstem respiratory nuclei involved in respiratory rhythmogenesis and chemosensitivity, including the pre-Bötzinger complex, nucleus raphe pallidus and nucleus raphe obscurus; the same nuclei are also impaired in DLB, although less severely than in MSA [91]. In addition to the reduced ventilatory response to hypercapnia, and in line with PD, respiratory dysfunctions in DLB also comprise both impaired cough reflex and UTC responses [92–94]. In particular, UTC seems to be controlled by the insula, a region primarily and critically involved during DLB progression [94].

Inspiratory stridor is probably related to vocal cord paralysis or vocal cord and laryngeal dystonia, leading to glottis closure [95, 96], and the presence of nocturnal stridor is classically considered an important predictor of sudden death in these patients [97]. No data about the role of dopaminergic therapy or DBS are available in MSA, and some authors proposed an approach with CPAP or botulinum toxin injection into vocal cords [98, 99]. Obstructive sleep apnoea has been related to pharyngeal narrowing due to brainstem neurons degeneration [100], and similarly to other forms of obstructive apnoea CPAP is the preferential treatment.

Among tauopathies, respiratory dysfunctions have been investigated in PSP, where a critical impairment of voluntary respiratory control has been reported, while automatic and limbic control seem to be preserved; accordingly, nocturnal respiratory abnormalities were not found even in the most severely disabled patients [101, 102]; in particular, the conflict between volitional and automatic breathing in PSP may explain the "respiratory ataxia" sometimes described in these patients [102].

Practical recommendations for the clinician

Neurological and pneumological dysfunction are strictly connected in PD patients. Pneumologists should be aware that breathing problems in this class of patients may be a direct consequence of disease

progression and/or of the dopaminergic stimulation, as already mentioned for dyspnoea due to levodopa-induced diaphragmatic dyskinesias. Moreover, pneumologists should consider the spirometric abnormalities that could be found even in the early stages of the disease, and the potential therapeutic role on the airways function exercised by dopaminergic stimulation more than that seen with conventional inhaled drugs. Neurologists, in the same way, should always consider the role of pneumological evaluation in the clinical history of a PD patient and focus on respiratory function as a potential therapeutic target to improve quality of life in a patient complaining of breathing disturbances. Finally, the physician should remember also the potential benefit of pulmonary rehabilitation on functional respiratory tests and exercise tolerance even in the early stages [103], and it is reasonable to consider a respiratory training program in parallel with dopaminergic therapy in patients who report respiratory symptoms.

Conclusions

PD is frequently associated with respiratory disturbances, even in pre-motor stages and these should be considered as a part of the disease itself rather than a different problem. In this view, the presence of breathing symptoms should alert the physician of a PD not well controlled or in progression. Even if the role of anti-Parkinsonian drugs is still controversial, it should be considered that they may have a potential role in ameliorating pulmonary function as well as the possible negative contribution to muscle incoordination and worsening of shortness of breath in patients experiencing dyskinesias.

DBS may be considered for PD, and stimulation of the STN does not significantly impair respiratory drive, when delivered at low frequencies and short pulse width, even if no data are currently available on novel DBS targets and the development of respiratory alterations. In the near future, new targets such as the PPN may induce a better control of axial motor symptoms, potentially avoiding respiratory changes at the same time.

Finally, the presence of respiratory symptoms should be considered in patients with other form of Parkinsonism, even if more systematic studied are needed to investigate this topic, as well as needing more proof of the exact impact of a dopaminergic beneficial role in respiratory dysfunctions.

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