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ABSTRACT

Patients with Parkinson's disease are at risk for pulmonary complications as a consequence of both the underlying disease pathology and the side effects of medication. Degeneration of the substantia nigra and subsequent loss of dopaminergic neurons may produce changes in ventilatory parameters. Upper airway obstruction and chest wall restriction are both common, and both may respond to levodopa. However, therapy for Parkinson's may also contribute to pulmonary morbidity. Overtreatment with levodopa causes respiratory dyskinesia that may be difficult to differentiate from complications of the disease itself. Therapy with ergot derivatives may cause pleuropulmonary fibrosis. Pneumonia resulting from the respiratory complications remains a significant cause of morbidity and mortality in Parkinson's disease.

KEYWORDS: Parkinson's disease, dopaminergic, levodopa, chest wall rigidity, pulmonary complications

Objectives: Upon completion of this article, the reader should: (1) be able to discuss the common respiratory complications of Parkinson's disease; (2) know what pharmacotherapies are available to treat these complications; and (3) know potential complications of the medications used to treat Parkinson's.

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Parkinson's disease (PD) results from degeneration of the substantia nigra and loss of dopaminergic neurons. The cardinal manifestations of PD include tremor, rigidity, bradykinesia, and loss of postural reflexes. These abnormalities are not limited to the extremities but also affect striated muscle within the upper airway and chest wall. Noting this association in his early description of PD, James Parkinson described a man who, in addition to the cardinal features of the disease, "fetched his breath rather hard."[1] Medications used to treat parkinsonism are also associated with various pulmonary complications. Awareness of the spectrum of pulmonary manifestations of PD may allow clinicians to better care for their patients with this degenerative condition.

UPPER AIRWAY OBSTRUCTION

The most common manifestation of upper airway involvement in PD patients is hypophonia.[2] Reasonable estimates suggest that approximately 70% of PD patients are bothered by this symptom. Hypophonia re-

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sults from both rigidity and fatigability of the thyroarytenoid muscles during vocalization.[3,4] Although the neurological substrate of hypophonia has not been defined, a central cause is likely because lesions within the basal ganglia may adversely affect speech volume.[5,6] Treatment with anti-parkinson medications may partially alleviate the hypophonia, and speech therapy is generally recommended. Collagen injection into the vocal cords has also been tried with some success.[7]

Spirometry reveals that a high percentage of PD patients have upper airway obstruction (UAO), often in asymptomatic individuals.[8] This silent abnormality, coupled with the impaired cough reflex in PD patients,[9] may contribute to complications such as aspiration pneumonia. Two main types of UAO have been described. The first, termed respiratory flutter, is characterized by a pattern of UAO with superimposed rapid oscillations of the supraglottic structures and vocal cords that are apparent on a flow volume loop.[10] These rhythmic oscillations are time-locked to the 4 to 8 Hz resting tremor in PD patients and can be verified by endoscopy. The second pattern of UAO is characterized by irregular, abrupt changes on the flow-volume loop, at times indicating complete obstruction.[10] Rigidity and hypokinesia of both the upper airway and the chest wall are thought to contribute to this second pattern. As with hypophonia, UAO is thought to be a direct consequence of the pathology within the basal ganglia causing irregularities in agonist and antagonist respiratory muscle actions.

Both the overall prevalence of upper airway symptoms and physiological evidence for UAO in PD appear to be diminishing, which may reflect a therapeutic benefit of anti-parkinson medications on pulmonary status.[10–12] However, the prevalence of upper airway changes in PD may be decreasing simply because diagnostic accuracy is improving, and patients with UAO due to other causes are being more reliably excluded. Early reports may have demonstrated high percentages of UAO due to inclusion of patients with postencephalitic parkinsonsism, a condition that is clinically distinct from idiopathic PD and is known to produce pulmonary problems.[13] Previous findings of increased obstructive abnormalities may also be due to poor control of factors such as smoking and chronic bronchitis.[11]

Two recent studies using similar, carefully controlled populations of patients reported substantially different rates of baseline UAO.[12,14] The first study found restrictive changes as the primary abnormality, seen in 85% of patients, and only one of 63 subjects had UAO. The second study noted that UAO was more prominent, with abnormal inspiratory and expiratory flow rates seen in 62% of patients. A major difference between these studies was that the first studied patients while they continued their medications, whereas the second held the medications. This suggests that UAO may be acutely sensitive to dopaminergic stimulation.

Additional studies have unequivocally demonstrated the favorable response of UAO to anti-parkinson medications. A study using spirometry in idiopathic PD compared patients on and off intravenous apomorphine (a short-acting dopamine agonist) and showed that UAO was particularly sensitive to dopaminergic stimulation.[15] Improvement was seen primarily in inspiratory and expiratory flow rates with only a minor improvement in maximal inspiratory pressure. Total respiratory resistance remained normal and did not change with apomorphine. A recent placebo-controlled trial using oral levodopa has also confirmed this finding.[16] In this latter study, patients who met criteria for UAO demonstrated an improved "sawtooth" flow-volume loop pattern as well as enhanced expiratory flow rates with levodopa treatment.

More evidence of the effectiveness of anti-parkinson medications in ameliorating UAO derives from the observation that acute UAO with stridor and respiratory failure occasionally develops when these medications are manipulated or withdrawn.[17–20] This is particularly important during the perioperative period or times of critical illness, when the inability to use typical oral medications, such as levodopa, can promote these complications. Intravenous apomorphine has been proposed as a useful intervention in this situation[21] but has limited availability in the United States. Early postoperative reinstitution of oral therapy, particularly around the time of ventilator weaning, may help to reduce this type of complication. Similarly, rapid changes in medication dosage should be avoided.

RESTRICTIVE ABNORMALITIES

Like upper airway abnormalities, restriction within the respiratory system is also thought to reflect the primary pathology of PD. For years, this was considered to be the only respiratory dysfunction present.[22–24] This probably reflected the more advanced disability of patients with PD prior to the widespread use of levodopa, so that the restrictive abnormalities were more obvious. Spirometric findings in those early patients were similar to those with peripheral neuromuscular conditions and this was interpreted as "muscle weakness."[22] Because myopathic weakness is not a feature of PD, most clinicians would reinterpret this finding as disordered central respiratory control and muscle fatigability, leading to apparent chest wall muscle weakness.

The restrictive changes of PD are also thought to be due to loss of chest wall compliance secondary to severe rigidity. Electromyographic assessment of the respiratory musculature supports this hypothesis.[25] In addition, longstanding chest wall rigidity may lead to kyphoscoliosis, substantially reducing lung volumes and contributing to restrictive ventilation.[14]

With the effective therapies of PD now available, restrictive changes are thought to contribute less to early

pulmonary disability. However, restrictive disease correlates with motor hallmarks of more advanced disease such as falls and gait freezing.[26] Because these motor manifestations are less responsive to dopaminergic stimulation, this suggests that the restrictive process may eventually become unresponsive to medical management. Also, kyphoscoliosis associated with PD rarely improves with medical management, and physical therapy interventions are recommended.

SLEEP APNEA

Sleep apnea is not thought to be associated with idiopathic PD.[27] However, a similar condition, now termed multiple system atrophy (MSA), is associated with a variety of nonextrapyramidal findings that may include sleep apnea. *MSA* is an encompassing term that currently includes diagnoses such as Shy-Drager syndrome, olivopontocerebellar atrophy, and striatonigral degeneration. MSA may have signs and symptoms of autonomic disturbance, spasticity, ataxia, neuropathy, and dementia, in addition to bradykinesia and rigidity. The parkinsonism in MSA is generally poorly responsive to medication. MSA is associated with a shorter life expectancy compared with idiopathic PD, possibly due to the concurrence of nocturnal stridor and central sleep apnea.[28] The pathophysiology of the sleep apnea in MSA is unknown, but may reflect the impaired autonomic control of the dorsal medullary respiratory center.[29] This type of UAO is generally unresponsive to dopaminergic modulation and is better treated by tracheostomy.

ACUTE COMPLICATIONS WITH MEDICATIONS

Although levodopa therapy improves respiratory and motor function in PD patients, development of dyskinesias (e.g., abnormal involuntary movements well recognized in advancing PD), may also affect ventilation. Patients with respiratory dyskinesias may complain of dyspnea and chest pain shortly after levodopa administration.[30,31] Serial pulmonary function tests and inductive plethysmography demonstrate the appearance of rapid shallow breathing and a decline in pulmonary function. These are associated with the clinical onset of limb and orofacial dykinesias that are typical of peak-dose, levodopa-induced dyskinesias. Because complaints of acute chest pain and shortness of breath in this older population might otherwise lead to an extensive evaluation for cardiac and pulmonary disorders, this side effect of treatment should be considered early in the differential diagnosis. A recession of the dyskinesias with medication withdrawal or dosage reduction is helpful diagnostically.

In more advanced patients, a wearing-off phenomenon between levodopa doses may induce acute pulmonary complaints, including dystonia of the laryngeal muscles causing stridor.[32] Chest wall tightness with shortness of breath and anxiety may also occur, which superficially resembles a panic attack.[33] This may be due in part to a psychological response to the sudden appearance of chest wall rigidity that causes an acute restrictive condition, but the reaction is not entirely psychological. These types of wearing-off phenomena are treated similarly to other motor fluctuations.[34] Generally, the strategy is to smooth the levodopa response by providing appropriate dose overlap or adding a dopamine agonist or catechol-o-methyltransferase inhibitor to provide longer-acting therapy.

PLEUROPULMONARY FIBROSIS

Another complication of PD therapy is the development of pleuropulmonary fibrosis induced by dopamine agonists like bromocriptine.[35,36] This is thought to be a specific response to the ergot dopamine agonists and, therefore, is not seen with newer agents like pramipexole and ropinerole. Symptoms include dyspnea, pleuritic pain, and a nonproductive cough. Pulmonary infiltrates and pleural effusions are seen on the chest radiograph. The sedimentation rate may be elevated and the pleural fluid may show inflammatory cells with a predominance of eosinophils. Although initially believed to be present in 2 to 5% of patients on the ergot agents, this condition is now thought to be exceedingly rare.[37,38] Discontinuing the dopamine agonists usually reverses the abnormalities. The pathophysiology for this entity is poorly understood but may reflect serotonergic activation triggering an inflammatory response.[39] More recently, a link between this response and prior exposure to asbestos was postulated.[40]

EXERCISE CAPACITY AND VENTILATORY STATUS

Although most patients with respiratory impairment associated with PD are asymptomatic, these studies suggest increased disability corresponding to the level of respiratory dysfunction.[26] Whether the respiratory abnormalities contribute to the disabilities or are simply markers for more advanced disease is unknown.[8] However, short-term pulmonary rehabilitation and exercise programs may improve some respiratory parameters and exercise capacity in ambulatory PD patients, with the expectation that quality of life would be improved, as well.[41,42] These data, coupled with evidence suggesting abnormalities in repetitive ventilatory tasks in early patients,[43] support the concept that the already high prevalence of abnormal resting pulmonary function tests in more advanced PD patients may still underestimate the importance of respiratory difficulties in this population. It is prudent to consider abnormal ventilatory status in

any PD patient who complains of excessive fatigue and poor exercise tolerance because these complaints might be amenable to nonpharmacological therapy. Arterial blood gases may occasionally detect hypoventilation, although studies on the response of Parkinson's patients to noninvasive ventilation are lacking.

ASPIRATION PNEUMONIA

As Parkinson's disease progresses, respiratory impairment becomes more severe. Mastication is affected, brady- and dyskinesias impair the swallowing mechanism, and aspiration becomes a problem. Switching to a soft mechanical diet, and the input of a speech and swallowing therapist may help. Patients are taught to chew carefully and to maintain a chin tuck position while swallowing. However, these measures are temporizing, and patients may have difficulty learning the swallowing techniques if their Parkinson's is complicated by dementia.

Eventually, the cough mechanism becomes weakened by chest wall rigidity, dyskinesias, and upper airway dysfunction. This, in combination with the swallowing difficulties, creates a lethal situation, leading inevitably to aspiration pneumonia and death. Tracheostomy can be used to treat the swallowing and cough impairment but is not recommended in patients with advanced disease, particularly if complicated by dementia.

CONCLUSIONS

Pneumonia remains the most frequent cause of death in PD patients despite the development of effective therapeutic regimens over the past three decades. The reason for the lack of a greater therapeutic effect is multifactorial. The primary pathological defect in PD, the destruction of the substantia nigra and loss of dopaminergic neurons, combined with the side effects of the medications used to treat the condition, affect the pulmonary system at multiple levels. These defects contribute to impairment of upper airway function as well as chest wall compliance and lead to problems with swallowing and cough that predispose to the development of pneumonia, the leading cause of mortality in PD. In addition to optimal medical therapy that helps to improve upper airway function, measures aimed at enhancing cough and reducing the risk of aspiration may help. Ultimately, further advances in the medical therapy of PD should reduce the morbidity and mortality attributable to pulmonary dysfunction, leading to better outcomes for individuals suffering from this progressive neurodegenerative condition.

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