Rapid onset of pergolide-induced pulmonary fibrosis in a patient with corticobasal degeneration

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INTRODUCTION

This article reports a patient with corticobasal degeneration (CBD), a rare disease, who presented with a short history of increasing dyspnoea, attributed to pulmonary fibrosis caused by pergolide. Only brief case series have previously reported this reaction. This case highlights key clinical features in extrapyramidal syndromes that are indicators of possible alternative diagnoses to Parkinson's disease (PD). With increased awareness of such diagnoses, unnecessary drug prescription and side effects may be avoided.

PD is a clinical diagnosis, based upon the presence of the four cardinal features of bradykinesia, rigidity, tremor and loss of postural reflexes. Drug treatment for PD commonly includes the use of dopamine agonists as well as levodopa, but these drugs are not as effective in the management of other neurodegenerative diseases that can mimic PD and are not routinely prescribed. The side-effect profile of the ergoline dopamine agonists such as pergolide includes pleural, pericardial and retroperitoneal fibrosis. Pulmonary fibrosis is less commonly reported. Physicians need to be aware of the side effects of these drugs as earlier recognition and withdrawal of the offending drug may significantly affect prognosis. This article reports a case of CBD initially diagnosed as PD where escalating doses of pergolide rapidly resulted in this rare side effect.

CASE REPORT

A 66-year-old man presented with gradually increasing dyspnoea and reduced exercise tolerance. There was no chest pain or any other respiratory symptoms, he had never smoked and there was no occupational exposure to dusts, toxins or asbestos. He also complained of a dull pain and numbness in his left forearm, unrelated to exertion.

Previous medical history included ischaemic heart disease and parkinsonism which was unresponsive to escalating therapy. Medication on presentation included aspirin 75 mg, pergolide 1 mg three times daily and two Sinemet plus three times daily.

He was apyrexial and tachypnoeic (respiratory rate 32/min), oxygen saturation 89% on air, the peak expiratory flow rate was 140 litre/min, heart rate 82 beats/minute and bloot pressure 143/66 mmHg. The jugular venous pressure was not raised and there was poor lung expansion with florid, bibasal, late inspiratory crackles to the midzones. He was bradykinetic with a marked coarse, jerky resting tremor in the left upper limb with quasi-purposeful involuntary movements and marked apraxia. There was greatly increased axial tone. No limb weakness was demonstrated, reflexes were unremarkable and the plantar response was flexor. There was sensory impairment in the left arm and leg to all modalities. His gait was bradykinetic and shuffling with retropulsion on stopping. He had a full range of eye movements with unrestricted vertical gaze.

Full blood count, urea and electrolytes, liver function tests, calcium and creatine kinase were all normal. His C-reactive protein level was 63 mg/litre and erythrocyte sedimentation rate was 45mm/hr. Arterial blood gas analysis on air revealed; partial pressure of arterial oxygen (PaO_2) 7.2 Kpa, partial pressure of arterial carbon dioxide ($PaCO_2$) 2.6 Kpa, pH 7.52, base excess 2, bicarbonate 26 mmol. An electrocardiogram showed sinus rhythm with Q waves in III and aVf.

Chest X-ray showed bilateral extensive subpleural interstitial changes and honeycombing with loss of volume particularly in the right lung (*Figure 1*). High resolution computed tomography of the thorax demonstrated widespread bilateral reticular shadowing suggestive of fibrosis, honeycomb changes and associated basilar traction bronchiectasis. Lung function tests demonstrated a forced expiratory volume in 1 second (FEV_1) 1.41 litres (52% of predicted), forced vital capacity (FVC) 1.45 litres (43% of predicted), FEV_1/FVC 97% and gas transfer factor (DLCO) 17.4 (70% of predicted).

He was treated with oxygen and antibiotics. Transbronchial biopsy with histology demonstrated diffuse fibrous tissue, with no evidence of infection, tuberculosis or malignancy. Bronchoalveolar lavage revealed a neutrophilia. Microbiology cultures were negative. His antinuclear antibody, complement levels, classical antineutrophil cytoplasmic antibody, rheumatoid factors, Scl-70 and Jo-1 antibodies were normal. Reviewing his medication with pharmacy led to the discontinuation of pergolide since it has been reported to cause diffuse interstitial pulmonary fibrosis. A consultant neurological review was sought and a diagnosis of corticobasal degeneration made.

He was discharged on home oxygen. After 1 month of discontinuing pergolide, the patient subjectively noticed improvement in his dyspnoea, reflected in an increase in DLCO (82% predicted).

DISCUSSION

The commonest cause of parkinsonism is PD. Certain clinical features or 'red flags' should alert the clinician to the possibility of an alternate diagnosis such as progressive supranuclear palsy, multiple system atrophy, or in this case CBD. The more important of these are lack of response to levodopa, a supranuclear gaze palsy, prominent early dysarthria, dysphagia or early dysautonomia and early falls. The presence in this case of cortical sensory loss and alien limb phenomenon in the context of a Parkinsonian syndrome particularly suggest a diagnosis of CBD.

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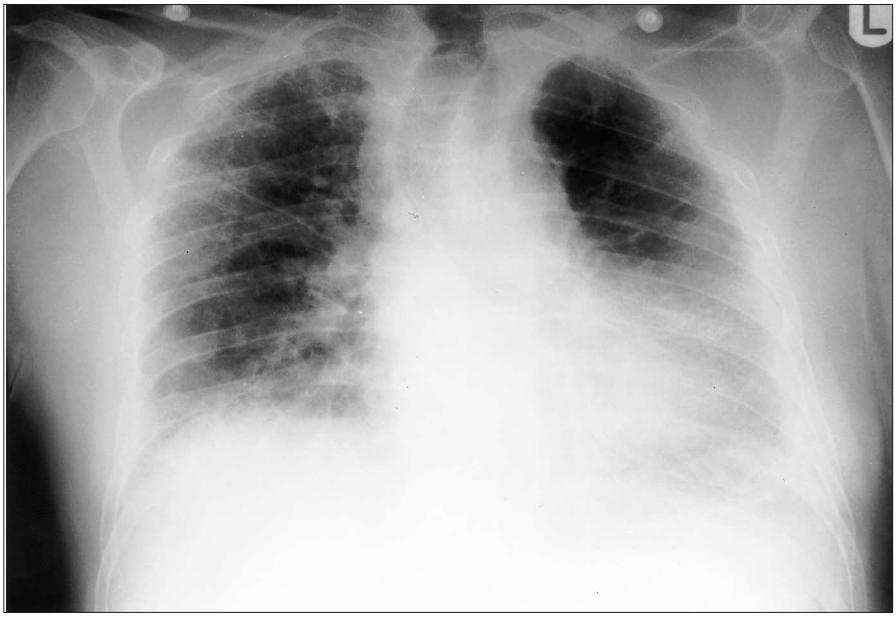
The first description of CBD was made in 1967 by Rebeiz et al. The disease is very rare and tends to be strikingly asymmetrical in presentation with stiffness, tremor and early muscular aches as suggested by Riley et al (1990) and Stover and Watts (2001). Limb dystonia is often a feature as are frontal release signs, aphasia, eyelid-opening apraxia, dementia and the alien limb phenomenon (a limb that manifests slow, involuntary wandering and quasi-purposive movements). Depression, anxiety, disinhibition and delusions also occur, as noted by Pillon et al (1995). Death, usually from bronchopneumonia, occurs 5–10 years after the onset of symptoms as Wenning et al (1998) have shown. Recognition of these conditions will result in less unnecessary prescribing and subsequent iatrogenic disease.

The diagnosis of drug-induced pulmonary fibrosis was made by a process of elimination and improvement after withdrawal of the offending agent. A previous series by Shaunak et al (1999) looked at pulmonary fibrosis associated with pergolide and found that symptoms emerged on average 2 years after the institution of treatment. This patient developed symptoms after a 6-month exposure. The mechanism by which pergolide causes fibrosis is not clear but is not dose dependant or related to duration of therapy as reported by Danoff et al (2001).

Pergolide is a synthetic ergoline dopamine agonist, acting on D_1 and D_2 receptors. A review (Anonymous, 2002) of the efficacy and safety of pergolide noted that it is associated with reactions common to all dopaminergic drugs such as nausea, vomiting, hypotension and psychosis. Recently, restrictive valvular heart disease has been reported in 26 of 76 PD patients treated with pergolide in a series by Van Camp et al (2004). In addition pleural pulmonary fibrosis has been reported by Lund et al (1999), Shaunak et al (1999) and Danoff et al (2001) but pulmonary fibrosis is only rarely reported.

Respiratory symptoms in a patient treated with pergolide or any other ergot derivative should alert the physician to the possibility of this complication. Other causes of interstitial lung disease must be excluded. High resolution computed tomography scanning is becoming increasingly helpful and may preclude the need for tissue diagnosis. **HM**

Figure 1. Extensive bilateral interstitial shadowing, honeycombing and loss of lung volume as a result of pulmonary fibrosis.



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