

## Combined pergolide-associated valvular heart disease and achilles tendon contractures

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Pergolide, bromocryptine, and cabergoline are ergot-derived dopaminergic (DA) agonists that have high affinity for the 5-HT<sub>2B</sub> serotonin receptor, which are expressed in heart valves and may mediate mitogenesis and subsequent proliferation of fibroblasts (1). Tendon deformities in Parkinson's disease (PD) patients are an uncommon complication (2) and preceded pergolide use (3). However, we describe a PD patient, who developed both progressive cardiac valvulopathy and severe Achilles tendon contractures after pergolide use. We hypothesize that this case supports the fact that PD patients may be patho-physiologically predisposed due to their inherent DA deficiency and that ergot-derived dopaminergic agonist drugs, such as pergolide cause secondary fibrotic stimulation via the 5-HT<sub>2B</sub> mechanism (4). Images of the fibrotic cardiac valvular pathology and Achilles contractures are demonstrated.

A 68-year old female with Parkinson's disease (PD) with right-sided predominant tremor was taking pergolide, 1mg four times a day orally for ten years. She was referred to our hospital for progressive heart failure, due to tricuspid and mitral valvular insufficiency. At that time, she had mild bilateral Achilles contractures and mild "off" dystonia. The Achilles tendons also appeared thicker than normal. Pergolide was discontinued and levodopa-carbidopa started in its place. The patient's heart failure progressed to require tricuspid and mitral valve replacement with bioprosthetic valves. Pergolide-associated mitral valve pathology (5) is shown (Figure 1).



Figure 1 Anterior leaflet excision of the patient's native mitral valve after surgery, showing the diffuse leaflet and chordal thickening, with focal subannular calcification, characteristic for pergolide-associated valvular disease. Underlying valve architecture was intact and undistorted. Microscopically (not shown), the valvular thickening was due to fibroproliferative tissue encasing the tendon and its cords and spreading primarily along the ventricular surface of the leaflet, associated with an abundant extracellular matrix that was rich in collagen and contained lesser amounts of elastin.



Figure 2 Anterior view just off the midline of the plantar flexor, inversion contractures with shortening of the Achilles tendon and thickening of the overlying skin.

However, over the following three years, the patient's Achilles tendon contraction deformities progressed out of proportion to her dystonia (2) (Figure 2), impairing her ambulation, which required a walker. Her Parkinson's tremor, however, was well controlled on levodopa-carbidopa orally.

Physical therapy was attempted for Achilles tendon stretching, and with ankle-foot braces. Botulinum toxin injections into the gastrocnemius were even attempted but did not help release the Achilles tendon contractures. MRI of the brain was normal for age, with only mild small vessel changes (Figure 3). Achilles tendon surgery was ultimately performed to release the tendon contractures and improve her ambulation.

Limb deformities associated with PD were originally reported by Charcot in 1877 (3) and were likely dystonic in nature. However, literature cites that dystonic limb deformities may be accelerated by ergot-derived dopamine agonists, bromocriptine and pergolide (3), but the exact pathologic mecha-

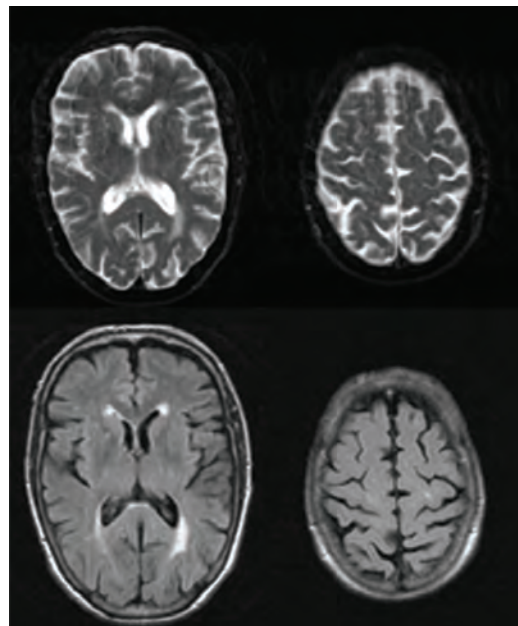


Figure 3 MRI of the brain. The upper images show T2 sequences, and lower images FLAIR sequences, demonstrating periventricular hyperintensities consistent with small vessel disease. Otherwise the MRI brain study, and in particular the basal ganglia, were normal.

nism has remained unclear. To our knowledge, this is the first case report of combined fibrotic disease of the heart (valvular) and exacerbated limb contractures associated with an ergot-related dopamine agonist (pergolide). The Food and Drug Administration voluntarily removed pergolide from the US market due to increasing reports of valvular disease. Fibrotic complications are sometimes reversible after discontinuation of the ergot-derived dopamine agonists, but not in all cases (6), such as some cases of retroperitoneal fibrosis and our case with Achilles tendon contractures.

Further, we feel these findings are particularly important given the known fibrotic complications of these dopaminergic ergot agents, and other retroperitoneal, pleural, pulmonary interstitial fibrosis may be overlooked and attributed to dystonia alone, which was not the sole cause of our patient's severe Achilles tendon contracture. This case may yield further insight into the poorly understood fibrotic pathophysiology between serotonin 5-HT<sub>2</sub> and dopaminergic pathophysiology (1, 4).

We hypothesize that Parkinson's disease is an inherent dopaminergic state, which when exposed to non-selective ergot-derived dopaminergic agonists which secondarily stimulate 5HT(2B) leads to fibrotic stimulation. As further support of this hypothesis, the dopaminergic agent lisuride has been shown to be an extremely potent 5-HT(2B) antagonist, where no cases of cardiac valvulopathy have ever been reported,

in more than 360,000 patient years (4). The molecular basis for this requires further study.

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