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LETTER TO THE EDITORS

Reversible cardiac valve fibrosis secondary to treatment with high-dose cabergoline for Parkinson's disease

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Dear Sirs,

When first presenting in June 2006 at the movement disorders clinic, the patient, a 51-year-old gentleman, was under treatment with cabergoline after having been diagnosed with Parkinson's disease (PD) of the akinetic rigid type 2 years ago. He was in good state of health, but he complained about progressive shortness of breath when climbing stairs, which had started a few weeks previously. On auscultation, a 3/6 diastolic murmur was noted in the aortal valve area. An immediately performed echocardiography showed fibrosis and thickening of the tricuspid, mitral and aortic valves, a second-grade insufficiency of the mitral and aortic valves and a borderline size of the left ventricle (Fig. 1). The patient reported that he had gradually increased his dose of cabergoline to 26 mg/day within the past year without approval of his treating neurologist. He did so in order to minimize the impact of motoric limitations due to PD and to be able to participate in the local tennis championships. This dose enabled him to perform at the same level as before the diagnosis of PD. Cabergoline was discontinued instantly and replaced by levodopa and amantadine. In summary, he had taken a cumulative dose of 8,353 mg cabergoline since the therapy had been initiated 20 months before. In July 2005, 1 year before presentation at the movement disorders clinic, echocardiography was performed. The daily dose of cabergoline at that time was 4 mg/day. A prolapse of the anteromedial leaflet of the mitral valve was noted, otherwise the examination was unremarkable. Based on this study, continuation of the therapy with cabergoline was assessed to be safe.

The course of the cardiac examinations is shown in Fig. 1. Despite discontinuation of cabergoline, echocardiography showed a deterioration of the affected valves in November 2006 and February 2007. Along with these echocardiographical findings the clinical condition of the patient worsened until February 2007, when he reported progressive dyspnoea when climbing stairs. At this time complete invasive cardiac evaluation including aortography, ventriculography and coronary angiography confirmed the echocardiographic diagnosis. Based on severity of symptoms (NYHA III), and based on the diagnostic findings, surgical replacement of the aortic and mitral valves was recommended. However, the patient insisted to remain on conservative therapy including frequent re-evaluations of his cardiac condition. In April 2008 the patient reported having recovered from the shortness of breath when climbing stairs and echocardiography was significantly improved (Fig. 1). By December 2009, echocardiography showed a continued improvement, which was accompanied by an almost complete recovery of his physical condition allowing the patient to start playing tennis again.

Because of cardiac side effects, ergot-type dopamine agonists are no longer considered as first line treatment of PD [1–5]. However, the incidence of dopamine agonists induced cardiac fibrosis remains under discussion [3].

The excessive dose of cabergoline in our case suggests a dose dependent effect on the development of cardiac fibrosis, which has been suggested for pergolide before [6]. The pathogenic mechanism of cardiac valve fibrosis involves the stimulation of 5-HT2b receptors by dopamine

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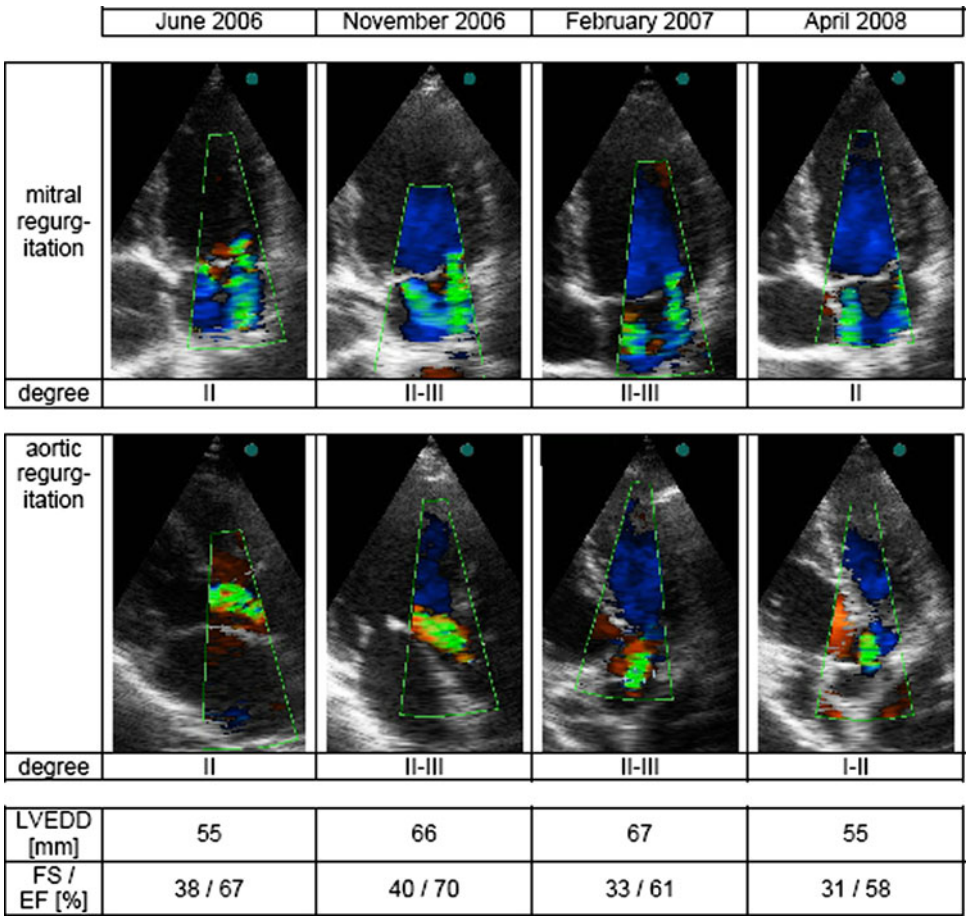

Fig. 1 Colour Doppler sonography images of mitral (*above*) and aortic (*below*) valves from June 2006 to April 2008. Corresponding values of left ventricular end diastolic diameter (LVEDD), fractional shortening (FS) and ejection fraction (EF) are provided. While the exact quantification of regurgitation by colour Doppler remains methodically difficult, and can be best compared only within the same patient (as we show), the increase of the ventricle diameter in M-mode is a very precise and reproducible measurement that helps to quantify changes in the underlying pathogenic condition. In June 2006 the cardiac valve fibrosis was diagnosed and cabergoline replaced by levodopa. In November 2006, a continuing deterioration of mitral and the aortal valve disease with valve incompetence of grade II–III° was observed. The size of the left ventricle was increased to an end-diastolic diameter of 66 mm. The condition continued to deteriorate until February 2007 when surgical valve replacement was recommended. Fourteen months later, in April 2008, a significant improvement was observed

agonists in cardiac valve tissue, which leads to the growth of collagen fibres and thereby to thickening, shortening, and reduced mobility of the valves [4].

It is unknown whether the dopamine agonist induced cardiac fibrosis is reversible [3]. This case, followed carefully by neurologists and cardiologists, confirms observations of other cases [5], that clinical cardiac condition and valve disease continued to deteriorate even after cessation of treatment with dopamine agonists. However, if the stimulation of 5-HT2b receptors is eliminated, even severe fibrotic changes of heart valves induced may improve over time [5]. This has been observed for fibrotic changes induced by pergolide [5] and is now reported for cabergoline for the first time. Therefore, in selected clinically stable patients, delaying valve surgery allowing for spontaneous recovery of valvular function may be justified.

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Conflict of interest None.

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