CASE REPORT

Cabergoline-associated valvulopathy of the tricuspid valve in the treatment of prolactinoma

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Summary

Cabergoline-associated valvulopathy (CAV) is defined by the echocardiographic triad of moderate or severe regurgitation, valvular thickening and restricted valvular motion. While it is a well-described complication of dopamine agonist therapy in Parkinson's disease, only three convincing cases of CAV have previously been described in the treatment of prolactinoma, with none involving the tricuspid valve. We describe a case of CAV affecting the tricuspid valve, ultimately resulting in the patient's death. The novel finding of CAV affecting the tricuspid valve suggests a possible link between confirmed cases of CAV and the echocardiographic surveillance studies of cabergoline-treated prolactinoma patients which have mostly demonstrated subclinical tricuspid valve changes. The risk of CAV, although small, prompts a mindful prescription of dopamine agonist therapy for prolactinomas and consideration of measures to minimise cabergoline exposure. The cumulative cabergoline doses and duration of therapy associated with CAV in published cases exceed what has been evaluated in case series and surveillance studies, underscoring the importance of case reports in understanding CAV.

Key Words

- prolactinoma
- dopamine agonist
- cabergoline
- valvulopathy
- tricuspid
- cabergoline-associated valvulopathy

Learning points:

- Cabergoline-associated valvulopathy is a rare but serious complication in the treatment of prolactinoma. Its rarity among treated patients may lead to a general acceptance that medical treatment is completely safe, but this may not be the case in those reaching high cumulative doses.
- Potential surveillance strategies include baseline echocardiography, followed by periodic clinical examination, and serial echocardiography every 1–5 years depending on risk and dopamine agonist exposure.
- Long-term management strategies – chiefly surgery, sometimes radiotherapy – should be considered in patients to minimise overall cabergoline exposure.

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Background

Prolactinoma is the most common functional tumour of the pituitary. The prevalence of clinically apparent prolactinoma ranges from 10 to 50 per 100,000 (Melmed *et al.* 2011). Dopamine agonist (DA) therapy is currently recommended as first-line therapy in prolactinoma. Cabergoline, an ergot-derived DA, is the preferred agent in the treatment of prolactinoma because of its high efficacy and tolerability (Melmed *et al.* 2011).

Cabergoline-associated valvulopathy (CAV) is a well-established complication in the treatment of Parkinson's disease, but its occurrence is very rare in the treatment of hyperprolactinaemia (Caputo *et al.* 2015). CAV is defined by the echocardiographic triad of moderate or severe regurgitation, valvular thickening and restricted valvular motion. The pathogenesis of CAV has been attributed to the stimulation of the 5-HT_{2B} receptors on cardiac valves, which mediate mitogenesis, fibroblast proliferation and remodelling (Caputo *et al.* 2015, Stiles *et al.* 2021). This results in valvular fibroplasia, a similar process to that of carcinoid syndrome (Schade *et al.* 2007). Thus far, three confirmed CAV cases have been reported in the prolactinoma literature, none of which have involved the tricuspid valve (Cawood *et al.* 2009, Gu *et al.* 2011, Caputo *et al.* 2018).

We present a historic case of CAV involving both the tricuspid and mitral valves in a patient treated for prolactinoma and resulting in the patient's death. This index case of tricuspid CAV is noteworthy as the tricuspid valve is the valve that most consistently shows alteration, albeit mild, in echocardiographic surveillance studies of cabergoline-treated prolactinoma patients. The tricuspid valve is also of special interest because it contains the greatest density of 5-HT_{2B} receptors and is the most commonly excised valve in the setting of carcinoid heart disease (Stiles *et al.* 2019).

Case presentation

A 75-year-old man initially presented in 1975 at age 39 with a 4-year history of lethargy, cold intolerance, reduced libido and erectile dysfunction. Examination demonstrated bitemporal hemiachromatopsia. He had no significant past medical history. Hypocortisolism, hypothyroidism and hypogonadotropic hypogonadism were confirmed biochemically. The pituitary fossa tomogram demonstrated depression of the left side of the pituitary fossa, suggestive of a pituitary macroadenoma. He was commenced on cortisone acetate, thyroxine and testosterone replacement, with symptomatic improvement.

Prolactin had been recently identified in humans in 1970 by HG Friesen (Melmed *et al.* 2011), and measurement was not available locally until 3 years after the patient's diagnosis. At this stage, serum prolactin was found to be 132-fold normal at 1590 μg/L (reference range 0–12 μg/L).

Visual deterioration and growth of the tumour on serial computed tomography (CT) prompted surgical resection 5 years after the initial presentation. Transsphenoidal hypophysectomy was performed in 1980, allowing decompression of the optic chiasm. Histology demonstrated a predominantly chromophobe adenoma with few mitoses.

Postoperatively, prolactin fell from 1892 to 670 μg/L (reference range 0–12 μg/L), and residual tumour was suspected on CT. Bromocriptine was commenced at 2.5 mg bd and uptitrated over 19 years until intolerance developed, particularly somnolence. In 2000, bromocriptine was changed to cabergoline 2 mg twice weekly which was well tolerated. Stable prolactin levels allowed gradual weaning to 750 μg per week over the next 8 years.

A routine clinical review of the patient in 2008 at age 72 revealed new-onset decompensated right ventricular failure with 3 months of bilateral ankle oedema, paroxysmal nocturnal dyspnoea and atrial fibrillation with a pansystolic murmur and elevated jugular venous pressure.

Investigation

Echocardiogram confirmed a thickened and restricted tricuspid valve with failure of leaflet coaptation resulting in severe regurgitation (Fig. 1). The right atrium was severely dilated and right ventricular function was mildly impaired. The mitral valve was also thickened, with moderate-to-severe regurgitation and moderate dilation of the left atrium. Findings were similar to that seen in carcinoid syndrome and consistent with CAV. There was no baseline echocardiogram for comparison, noting cabergoline commencement pre-dated the recognition of CAV (Schade *et al.* 2007).

A primary diagnosis of CAV was made. At this point, the total cumulative cabergoline dose was estimated to be 782 mg. Cabergoline was then changed back to low-dose bromocriptine.

Repeat MRI demonstrated a 27 mm pituitary macroadenoma with no chiasmal compression. Pituitary

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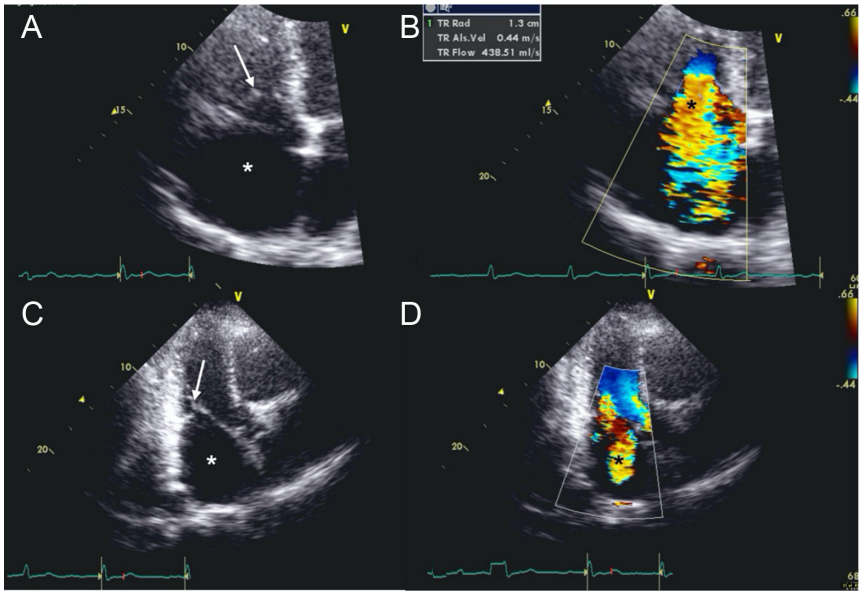

Figure 1
(A) The tricuspid valve leaflets are thickened and restricted with failure of coaptation (arrow). The right atrium is severely enlarged (*). (B) Colour Doppler across the tricuspid valve demonstrates severe tricuspid regurgitation (*) with a proximal isovelocity surface area radius of 1.3 cm. (C) The mitral valve leaflets and chordae are thickened and shortened and do not coapt completely (arrow). The left atrium is moderately enlarged (*). (D) Colour Doppler across the mitral valve shows severe mitral regurgitation (*), which was corroborated by other measures of severity.

surgery was not pursued given the patient's cardiac deterioration and lack of neuro-ophthalmic compromise. He underwent fractionated radiotherapy, receiving a total of 45 Gy. As serum prolactin continued to rise, low-dose bromocriptine was continued. Concurrently, the patient was treated with perindopril, spironolactone and furosemide for cardiac failure, and digoxin and warfarin for atrial fibrillation.

Serial echocardiography demonstrated progressive and severe right atrial dilatation, moderate right ventricular dilatation and progression of mitral regurgitation from moderate-severe to severe. Left ventricular size and function remained normal with an ejection fraction of 69%.

Treatment

Mitral and tricuspid valve repairs were ultimately recommended. Preoperative evaluation confirmed normal pulmonary pressures and left coronary artery system, with a stenosed right coronary artery. In 2011, mitral and tricuspid valvular repairs were performed along with coronary artery bypass grafting to his right coronary artery. A severely dilated tricuspid annulus was noted intraoperatively, although no comment was made on the valve appearance. No histology was available for analysis.

Outcome and follow-up

The patient died in the hospital 49 days postoperatively. His gradual deterioration was multifactorial, including anasarca, hospital-acquired pneumonia and multi-organ failure.

Discussion

The three case reports of CAV published thus far have involved the mitral and aortic valves (Cawood *et al.* 2009, Gu *et al.* 2011, Caputo *et al.* 2018) (Table 1). The case reported herein is the first description of the full echocardiographic triad of CAV to involve the tricuspid valve. This case provides insight into the possible pathophysiology of CAV, whilst the severity of valvulopathy, ultimately contributing to the death of the patient, underscores the importance of awareness of this risk amongst endocrinologists.

To date, there has been a disconnect in the prolactinoma literature between the multiple echocardiographic surveillance studies performed in cabergoline-treated patients and the few case reports of clinically apparent CAV (Schade *et al.* 2007, Gu *et al.* 2011, Stiles *et al.* 2019). Meta-analysis of surveillance studies has shown an increased risk of asymptomatic moderate tricuspid regurgitation in cabergoline-treated prolactinoma patients up to a mean follow-up of 7 years, without evidence of any other valvulopathy (Stiles *et al.* 2019). Notably, these data were collected without standardisation of echocardiographic measurement and also lack detail regarding valve morphology and mobility (Stiles *et al.* 2019). It is unclear if this finding in the absence of the remaining diagnostic triad represents an early, pre-symptomatic stage of CAV or is unrelated (De Sousa 2022).

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Table 1 A summary of known cases of cabergoline associated valvulopathy in the prolactinoma setting.

	Age	Valve	Prior bromocriptine therapy	Duration of cabergoline therapy	Total cumulative dose	Echocardiogram	Valve histology
Cawood *et al.* (2009)	61 years	Mitral	None	3 years	252 mg	MV: thickened and restricted leaflets, severe regurgitation	MV: fibroproliferative plaques with preservation of the underlying valve architecture
Gu *et al.* (2011)	Unknown	Mitral	8 years, cumulative dose 2780 mg	10 years	5252 mg	MV: thickened with asymmetric tenting, moderate regurgitation	No reported valvular surgery
Caputo *et al.* (2018)	50 years	Aortic	7 years, unknown cumulative dose	19 years	4192 mg	AV: thickened and restricted, moderate to severe regurgitation	No valvular surgery
Current case	72 years	Tricuspid and mitral	19 years, cumulative dose 146,495 mg	8 years	782 mg	TV: thickened, restricted, severe regurgitation MV: thickened, moderate to severe regurgitation	Valve repair only, no tissue obtained

AV, aortic valve; MV, mitral valve; TR, tricuspid regurgitation; TV, tricuspid valve.

By contrast, previous CAV cases in the prolactinoma setting have not involved the tricuspid valve. The index case of tricuspid CAV reported here provides a potential link between clinical cases of CAV and the surveillance studies in prolactinoma patients, although further CAV cases are required to substantiate this. All published cases of CAV in the prolactinoma setting are summarised in Table 1. Interestingly, two out of four cases occurred after total cumulative doses >4000 mg, comparable to those seen in Parkinson's disease, whereas the other two cases (including our case) occurred at far lower doses (Cawood *et al.* 2009, Gu *et al.* 2011, Caputo *et al.* 2018). CAV developed beyond the mean follow-up of previous case-control series in three out of four cases, although one case developed within 3 years of therapy (Cawood *et al.* 2009). Furthermore, three out of four cases involved prior bromocriptine which, as an ergot-derived DA and partial agonist of the $5HT_{2B}$ receptor, cannot be excluded in the pathogenesis of CAV (Elenkova *et al.* 2012). To date, no cases of clinically apparent valvulopathy from bromocriptine alone have been reported in the prolactinoma setting.

Endocrinologists should be cognisant of the risk of CAV. The reassuring results from most echocardiographic surveillance studies suggest that the risk is exceedingly small in patients receiving low-dose and short-term cabergoline treatment. However, patients receiving either high doses or prolonged treatment are at risk of developing CAV, which may have catastrophic consequences as shown here. To highlight the importance of considering both the dose and duration of cabergoline exposure, the cumulative dose of 782 mg reported in this case could be reached by 16 years of a low-dose regimen of 0.5 mg twice weekly or by 8 years of a regimen of 1 mg twice weekly. These durations exceed the length of previously published surveillance studies, but they are not unusual in clinical practice and can be difficult to predict when commencing therapy.

Screening for CAV should include periodic clinical examinations. However, the variation in total cumulative doses in the published cases makes it difficult to predict those most at risk. Baseline echocardiography is a highly valuable tool for later comparison and to identify the pre-existing valvular disease (Caputo *et al.* 2015, Stiles *et al.* 2021). Acknowledging this demand on resources, a potential strategy could be initial screening via examination, chest radiography and electrocardiogram to help identify patients requiring baseline echocardiogram. The debate as to the use and frequency of serial echocardiograms is ongoing. The accepted population at greatest risk is those aged over 50 or in whom total cumulative dose exceeds 520–720 mg (approximately 2–3 mg weekly for 5 years) (Caputo *et al.* 2015, Stiles *et al.* 2021). A reasonable

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approach would therefore include echocardiography at baseline and at 5 years, increasing thereafter. In the small number of patients treated on doses >2 mg/week, annual echocardiograms should be considered.

Clinically suspected CAV should be formally diagnosed using echocardiography to document the triad of moderate or severe regurgitation, valvular thickening and restricted motion. Given technician knowledge of DA therapy has been seen to bias echocardiogram reporting, echocardiogram grading systems have been developed to assist in bringing objectivity to the study (Gu *et al.* 2011, Stiles *et al.* 2021). Ideally, a latent or pre-symptomatic stage of the disease should be identified to allow for safe drug withdrawal. Early diagnosis of CAV with discontinuation of ergot-derived DA can allow recovery of valvulopathy, especially in monovalvular cases, or prevention of valvular deterioration, compared to drug continuation (Zanettini *et al.* 2011). Quinagolide, a non-ergot-derived DA has not been associated with this effect and may be considered as an alternative, particularly in aggressive tumours where medical treatment cannot be withdrawn (De Sousa 2022).

More broadly, the risk of CAV, although small, prompts a mindful prescription of DA therapy for prolactinoma. The goals of treatment primarily include tumour shrinkage, preservation of vision and restoration of gonadal function. Clinicians should aim for the lowest effective dose of DA but may require additional modalities. Tumour response to DA therapy, anticipated duration of therapy and total cumulative dose may help stratify risk and inform long-term management strategies for patients, including the option of pituitary surgery. In patients with persistent hypogonadism who are not seeking fertility, sex steroid replacement may be considered over complete normalisation of prolactinaemia. Consideration of DA withdrawal is important where appropriate to minimise overall cabergoline exposure and thus CAV risk.

Finally, this case highlights the importance of case reports in the study of CAV. Development of CAV appears limited to patients taking cabergoline at higher doses and/or for longer durations than what can be easily studied in systematic studies of prolactinoma patients. Follow-up review of patients in the initial case control studies may help clarify the natural history of pre-symptomatic regurgitation and its relation to DA therapy.

Declaration of interest
No conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
The patient reported and his next of kin are deceased; consent to publication therefore cannot be obtained. There is no known or likely reason the patient would not have consented, and his privacy and confidentiality have been preserved in this report. This is in line with the NHMRC National Statement on Ethical Conduct in Human Research.

Author contribution statement
AH wrote the manuscript, MS and AT reviewed the echocardiographic studies and manuscript, DT was involved in the patients care and reviewed the manuscript, SD conceived the paper and edited the manuscript.

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