Case Report Template

- All case reports MUST be submitted online using this template.
- Tables, images and multimedia files must be uploaded separately on submission.
- Articles should be no more than 2,000 words in length, and include a maximum of 10 references.
- It is essential that you list the learning points of the case; these are the messages that readers should remember when dealing with their own patients.
- We strongly encourage authors to comply with the CARE guidelines.
- You must have signed informed consent from patients (or relatives/guardians) prior to publication, using our consent form. Full details of our patient consent and confidentiality policy is available on our author guidelines page. Alternatively, Institutional Review Board approval of the manuscript as containing no identifiable information may be submitted with the manuscript in lieu of written consent by the subject of the report.

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**Title of case report or series**

Cabergoline-Associated Valvulopathy of The Tricuspid Valve in The Treatment of Prolactinoma

**Authors**

Provide all author names and affiliations. The corresponding author’s email address must be provided.

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**Summary**

Please provide a brief summary of the case report and context, which should be a single paragraph of no more than 250 words.

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 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.

**Learning points**

3 to 6 bullet points highlighting the take home messages of the reported case. These should be clear learning points which readers can use to inform medical education or clinical practice.

- 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 DA exposure.
- Long-term management strategies – chiefly surgery, sometimes radiotherapy – should be considered in patients to minimise overall cabergoline exposure.
Background
Outline why this case is important and of interest to other clinicians in the field. Does it describe an unusual or novel occurrence, or a common health problem? The types of cases of interest include:

- Findings that shed new light on the possible pathogenesis of a disease or mechanism of therapy
- Unique or rare presentations of a disease
- Novel diagnostic procedures or treatments
- New or unexpected associations between symptoms and diseases
- Presentations, diagnoses and/or management of rare or new diseases
- Challenging diagnosis
- Unusual or unexpected effects of medical treatment

Prolactinoma is the most common functional tumour of the pituitary. The prevalence of clinically apparent prolactinoma ranges from 10-50 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 stimulation of the 5-HT_{2B} receptors on cardiac valves, which mediate mitogenesis, fibroblast proliferation and remodelling (Stiles et al., 2021, Caputo et al., 2015). 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 an 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
Presenting features, symptoms and signs, relevant demographic information, relevant medical history of the patient. If it is a case series, then details must be included for all patients. Provide appropriate images, however patient confidentiality must be maintained wherever possible.

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. 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 three years after the patient’s diagnosis. At this stage, serum prolactin was found to be 132-fold normal at 1590 ug/L (reference range 0-12 ug/L).

Visual deterioration and growth of the tumour on serial computed tomography (CT) prompted surgical resection 5 years after 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 ug/L to 670 ug/L (reference range 0-12 ug/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 mcg per week over the next 8 years.

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

### Investigation
Results of any relevant tests that were carried out, in particular those influencing decisions on patient management.

Echocardiogram confirmed a thickened and restricted tricuspid valve with failure of leaflet coaptation resulting in severe regurgitation (Figure 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 MR imaging demonstrated a 27 mm pituitary macroadenoma with no chiasmal compression. Pituitary surgery was not pursued given the patient’s cardiac deterioration and lack of neuro-ophthalmic compromise. He underwent fractionated radiotherapy, receiving a total of 45Gy. 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 ejection fraction of 69%.

### Treatment
If relevant, provide a description of any treatment or intervention. Explain specific treatment decisions, including pharmacological and non-pharmacological. Give the generic name, dose and route of administration for drugs.

Mitrail and tricuspid valve repair was 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 repair 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
Provide follow-up data to enable readers to clearly understand the case outcome. Please specify follow-up period.

The patient died in hospital 49 days postoperatively. His gradual deterioration was multifactorial, including anasarca, hospital-acquired pneumonia and multi-organ failure.
Discussion
This should not be a summary of other similar cases. Authors should describe the points of interest of the reported case and discuss in the context of information available in the literature, with reference to relevant publications.

The three case reports of CAV published thus far have involved the mitral and aortic valves (Table 1) (Cawood et al., 2009, Gu et al., 2011, Caputo et al., 2018). 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 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 (Gu et al., 2011, Stiles et al., 2019, Schade et al., 2007). Meta-analysis of surveillance studies has shown 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).

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 prolactinomas 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, 2/4 cases occurred after total cumulative doses >4000mg, 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 ¾ cases, although one case developed within three years of therapy (Cawood et al., 2009). Furthermore, 3/4 cases involved prior bromocriptine which, as an ergot derived DA and partial agonist of the 5HT2B receptor, cannot be excluded in 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 0.5mg twice weekly or by 8 years of a regimen of 1mg 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 examination. However, the variation in total cumulative doses in the published cases makes it difficult to predict those most at risk. Baseline echocardiography is highly valuable tool for later comparison and to identify 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. 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) (Stiles et al., 2021, Caputo et al., 2015). A reasonable 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 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 mindful prescription of DA therapy for prolactinoma. 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.
Funding statement
Please detail all of the sources of funding relevant to the research reported in the following format:

'This work was supported by the Medical Research Council (grant numbers xxxx, yyyy); the Wellcome Trust (grant number xxxx); and Tommy’s Baby charity (grant number xxxx).’

Where research has not been funded please state the following: ‘This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.’

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Declaration of interest
Actual or perceived conflicts of interest for all authors must be declared in full. Please either (a) declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported; or (b) fully declare any financial or other potential conflict of interest.

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Patient consent
Include a statement confirming that written informed consent has been obtained from the patient (or patient’s guardian) for publication of the submitted article and accompanying images. Authors must also include a signed copy of our consent form in the patient’s notes for future reference. For full details, please refer to our patient consent and confidentiality policy within the author guidelines.

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 contributions and acknowledgements
Please include a statement specifying the contribution of each co-author. If the author is not the named physician of the patient please clarify involvement in the oversight of the reported case, or confirm you have permission of the physician who is responsible for the patient.

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.
References
Cite references in the text using the authors’ names and publication year. Use et al. for articles with more than two authors. Where there are several citations, list them in chronological order.

List references in the reference list in alphabetical order. For full details, please visit our author guidelines.


Legends to tables/figures/videos
Insert text of legends to any figures or tables. Tables, images and videos should be uploaded separately during online submission.

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 1.3cm. 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.

Table 1: A summary of known cases of cabergoline associated valvulopathy in the prolactinoma setting. TV: tricuspid valve, MV: mitral valve, AV: aortic valve, TR: tricuspid regurgitation.

Patient’s perspective
We welcome comments from your patient; their own description of their experience may help other patients or clinicians who are dealing with a similar problem. If your patient would like to contribute please...
Ensure they include only relevant personal details. Patients may describe their symptoms, how any tests and treatments affected them, and how the problem is now.
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 1.3cm. 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.
<table>
<thead>
<tr>
<th>Age</th>
<th>Valve</th>
<th>Prior Bromocriptine Therapy</th>
<th>Duration of Cabergoline Therapy</th>
<th>Total Cumulative Dose</th>
<th>Echocardiogram</th>
<th>Valve Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cawood 2009</td>
<td>61 years</td>
<td>Mitral</td>
<td>none</td>
<td>3 years</td>
<td>252mg</td>
<td>MV: thickened and restricted leaflets, severe regurgitation</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>MV: Fibroproliferative plaques with preservation of the underlying valve architecture</td>
</tr>
<tr>
<td>Gu 2011</td>
<td>unknown</td>
<td>Mitral</td>
<td>8 years, cumulative dose 2780mg</td>
<td>10 years</td>
<td>5252mg</td>
<td>MV: thickened with asymmetric tenting, moderate regurgitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No reported valvular surgery</td>
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<tr>
<td>Caputo 2018</td>
<td>50 years</td>
<td>Aortic</td>
<td>7 years, unknown cumulative dose</td>
<td>19 years</td>
<td>4192mg</td>
<td>AV: thickened and restricted, moderate to severe regurgitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No valvular surgery</td>
</tr>
<tr>
<td>Current case</td>
<td>72 years</td>
<td>Tricuspid and mitral</td>
<td>19 years, cumulative dose 146,495 mg</td>
<td>8 years</td>
<td>782mg</td>
<td>TV: thickened, restricted, severe regurgitation</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MV: thickened, moderate to severe regurgitation</td>
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<td></td>
<td>Valve repair only, no tissue obtained</td>
</tr>
</tbody>
</table>

**Table 1:** A summary of known cases of cabergoline-associated valvulopathy in the prolactinoma setting. TV: tricuspid valve, MV: mitral valve, AV: aortic valve, TR: tricuspid regurgitation.