The natural history of pituitary apoplexy: A long term follow-up study

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Abstract

**Background and Aims:** Pituitary apoplexy (PA) is a rare neurosurgical emergency, associated with deficiency of one or more pituitary hormones. Few studies have explored the relative outcomes associated with conservative and neurosurgical intervention.

**Methods:** A retrospective evaluation of all patients with PA reviewed at Morriston Hospital was undertaken and diagnosis was obtained from Morriston data base (Leicester Clinical Workstation (LCW) database) between 1998 to 2019 from clinic letters and discharge summaries.

**Results:** Forty-three patients with PA were identified with a mean age 74.1 years and 23 (53.5%) patients were female. Patients were followed up for a mean±SD 68.1±61.7 months. Twenty-three (53.5%) patients had a known pituitary adenoma. Commoner clinical presentations of PA were ophthalmoplegia or visual field loss. Following PA, 32 (74.4%) patients were noted to have a non-functioning pituitary adenoma. Neurosurgical intervention was taken in 17 (39.5%) patients of which 8 (47.1%) patients also received radiotherapy, 2 (4.7%) patients had radiotherapy alone and the remainder managed conservatively. External ophthalmoplegia recovered in all cases. Visual loss remained in all cases. One (2.3%) patient with chromophobe adenoma had a significant second episode of PA requiring repeat surgery.

**Conclusion:** PA often occurs in patients with undiagnosed adenoma. Hypopituitarism commonly occurred following conservative or surgical treatment. External ophthalmoplegia resolved in all cases however visual loss did not recover. Pituitary tumour recurrence and PA episodes are rare.

**Background**
Pituitary apoplexy (PA) is caused by haemorrhage or infarction of the pituitary gland and is often observed in the setting of a pituitary adenoma. This term was first introduced by Brougham et al in 1950, in a case series of 5 patients.\textsuperscript{1} Asymptomatic pituitary haemorrhage and/or infarction (subclinical pituitary apoplexy) may be detected in routine imaging or during histopathological examination in those with known PA, occurring in approximately 25%.\textsuperscript{2,3} The clinical presentation of PA is variable, but typically associated with acute severe headache, ophthalmoplegia, decreased visual acuity, visual loss, change in mental status, adrenal crisis, coma, or even sudden death.\textsuperscript{4} PA can result in serious long-term neuro-ophthalmic and endocrine complications. As PA is rare, there are no prospective trials undertaken to determine trial-based guidance to support management. Moreover, little consensus exists on the most appropriate management of this rare neuroendocrine emergency including whether conservative or surgical approach should represent first-line of treatment and the optimal timing of surgery. As such management is guided by the severity of the clinical presentation, expert opinion with local pathways and practices are cardinal in the management of PA.

**Methods**

This was a retrospective analysis of patients who presented with PA between 1998 and 2019 to the Endocrinology clinic at Morriston Hospital (Swansea). Permission was obtained from the local audit department to review prospectively collected data in clinic letters and electronic medical records at Endocrine database (LCW). Data were collected for demography, precipitating event, clinical presentation, whether there was a previous diagnosis of pituitary adenoma and the management including visual field
testing, conservative or surgical approaches to management, the indications for surgery and patient outcomes observed during follow-up.

Results
Forty-three patients were identified with PA over the study period: 23 (53.5%) female and 20 (46.5%) male patients with a mean±SD age 74.1±15.5 years (36-97 years). Patients were followed up for a mean 68.1±61.7 months (1-233 months). Presenting symptoms included acute visual field loss [23.3% patients], ophthalmoplegia [34.9% patients], headache [11.6% patients], cranial nerve palsy [11.6% patients], Cushing’s disease [2.3% patient], observed during routine CT scan without acute symptoms [11.6% patients] and as incidental MRI findings [4.7% patients]. This is presented in Figure 1.

A pituitary adenoma was previously diagnosed in 53.5% of patients, whilst 46.5% patients did not have a previously diagnosed adenoma. On review of the underlying pathology for PA; 74.4% patients had a non-functioning pituitary adenoma, 9.3% patients had malignant secondary’s, 7.0% patients had acromegaly, 4.7% patients had craniopharyngioma, 2.3% patient had Cushing’s disease and 2.3% patient had a macroprolactinoma. These data are presented in Figure 2.

Management and outcomes
Surgical management was taken in 17 (39.5%) patients, of which 5 (29.4%) required post-operative radiotherapy and 3 (17.7%) patients required further medical management followed by radiotherapy. Indications for surgery included visual field defects (n=10), persistent nerve palsy (n=2) and missing data in 5 patients. Most
patients [15, 88.2%] developed hypopituitarism post–operatively requiring multiple hormonal replacement. All patients who presented with external opthalmoplegia completely recovered irrespective of conservative or surgical approach.

Following PA, most patients developed at least one anterior pituitary hormone deficiency [33 (76.7%)]. Long-term steroid replacement was required in 26 (60.5%) patients, levothyroxine was required in 32 (74.4%), growth hormone replacement in 3 (7.0%) patients, testosterone replacement was prescribed to 8 (40.0%) male patients and desmopressin was required in 7 (16.3%) patients. Of the 3 (7.0%) patients with an underlying diagnosis of acromegaly, one (2.3%) was treated conservatively with radiotherapy as not fit for surgery. Resolution of acromegaly was observed post-operatively in a second patient, but the third patient unfortunately developed hypopituitarism. Outcomes are summarised in Figure 3.

Death was reported in three patients subsequently. One patient had an aggressive cromophobe adenoma with a second episode of PA and required repeat surgery. Two were treated conservatively for hypopituitarism. None of the patients died as a direct consequence of the pituitary apoplexy.

Discussion
In this study, important patient clinical characteristics and outcomes have been described for a relatively large number of patients compared with other case series. Moreover, the proportion of conservatively managed patients in this cohort [26 patients, 60.5%] is larger than most previously published case series. Observations from this descriptive case series include the support of a conservative approach in
selected patients with less severe and non-progressive neuro-ophthalmological deficits, in those without visual field deficits or whose visual fields are stable as neuro-ophthalmic complications in those patients largely resolved without the need for surgical intervention. Long-term follow up for patients who have secretory tumours is important as there is risk of persistence/recurrence of functional activity which may need early intervention.

Earlier published case series of patients with PA have advocated early neurosurgical intervention as the mainstay of treatment for classical PA. Reasons cited for earlier intervention include improved visual outcomes and better endocrine function in patients treated with early pituitary surgery. More recently, focus has generally shifted to carefully select patients as to whether surgical or conservative management is more appropriate. Indeed, one case series recently observed that visual and cranial nerve improvement rates were similar in those with PA treated conservatively or surgically. The data presented in this manuscript would support these findings, though our population had a greater proportion of cases treated conservatively (60.5% vs 26.9%)

Data presented in this case series demonstrates that carefully selected patients, such as those with less severe visual field deficits, can be managed effectively with a conservative approach with respect to neuro-ophthalmic outcomes comparable with those who are treated surgically at an early stage of presentation (within first week). These data add to the growing body of evidence that there is a place for conservative management and close observation in selected cases with acute PA with a similar outcome to surgery. Of course, by the definition of their selection the conservatively
managed cases will have less severe visual deficits and or cranial nerve palsy limiting comparisons between surgical and conservative management approaches.

In this cohort, at least, the prospect of recovering pituitary endocrine function following PA was low and did not appear to be influenced by the management strategy. The outcome was equally modest in both surgically and conservatively treated groups and similar according to whether surgery was early or delayed. Similarly, more recent case series of patients with PA\textsuperscript{12, 16, 17} have failed to replicate the recovery of pituitary function associated with surgical intervention described in earlier observations\textsuperscript{6, 15}. These data suggest that decisions on management strategy should not be influenced by the presence or severity of endocrine deficiencies at the time of presentation. The PAS was introduced in the UK Pituitary Apoplexy Guidelines for monitoring conservatively managed patients and as a tool for quantifying neuro-ophthalmological defects and to objectively assess the clinical severity of PA\textsuperscript{18}.

It has been shown that there is a significant risk of recurrence of pituitary tumours that undergo PA, necessitating long-term follow-up imaging\textsuperscript{18}. Non-functioning adenomas are the commonest type of pituitary adenoma to undergo PA. One study observed a pituitary tumour recurrence rate of around 11\% at 6.6 years follow-up for tumours managed surgically following PA which were not irradiated\textsuperscript{19}. Unfortunately, there are relatively few data describing recurrence rates of functioning pituitary adenomas following PA. One study described persistent hormonal activity or recurrence in three of four cases of Cushing’s disease initially treated conservatively, and in total, they noted that 5 of 16 secretory tumours recurred\textsuperscript{13}. In another study, tumour recurrence was observed in 1 case of Cushing’s disease out of a total of 7 secretory tumours\textsuperscript{19}. 
This underpins the need for long-term surveillance in an experienced unit and supports the recommendations made by consensus UK guidelines\textsuperscript{18} for at least annual follow-up in a joint neurosurgical and endocrine setting.

**Conclusion**

This is a relatively large case series of patients with PA from a single UK hospital with a significant period of follow-up. The data presented in this study demonstrate that a conservative approach to managing PA is appropriate in selected patients with less severe and non-progressive neuro-ophthalmological deficits. Nevertheless, early discussions with neurosurgical and endocrinology teams are essential. Patients with secretory tumours especially require long-term follow-up as the risk of persistence/recurrence of endocrine overactivity is high.

**References**


Figure legends

Figure 1

Figure 1 is a pie chart summarising the clinical presentation of the 43 patients identified with pituitary apoplexy. Data are shown as the percentage (%) of patients with each clinical presentation.

Figure 2
Figure 2 is a bar chart summarising the aetiology of the pituitary adenoma associated with PA. Data are presented as the number of patients with each aetiology of pituitary adenoma.

Figure 3

Figure 3 summarises the endocrine outcomes following PA. (a) is a bar chart summarising the outcomes in all patients with PA, and bar chart (b) summarises the hormonal replacement required by patients with hypopituitarism.