Hemorrhagic and Non-hemorrhagic Pituitary Apoplexy: Imaging Cohort Analysis

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Authors' contributions

This work was carried out in collaboration between all authors. Authors KOR and TBV designed the study and wrote the protocol. Author ED wrote the first draft of the manuscript and managed the literature searches. Authors JHM, ED, DP and DEM performed data collection. Author JHM performed statistical analyses. Author KOR managed the experimental process. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Patients suffering from pituitary apoplexy present with variable clinical symptoms and imaging findings. Imaging findings may differ between hemorrhagic and non-hemorrhagic apoplexy. Our study aimed to better define imaging findings in both hemorrhagic and non-hemorrhagic apoplexy and is the first cohort study to report a comparison of imaging findings in these two groups.

Materials and Methods: 311 consecutive patients admitted with pituitary tumors were retrospectively reviewed for clinical and imaging evidence of pituitary apoplexy. 37 operative cases were included in this cohort. A cohort statistical analysis was performed between the two groups using Chi Square, Fisher exact test, logistic regression, ANOVA, and t-test.

Results: Imaging analysis demonstrated a significant difference in the hemorrhagic cohort's
Computed Tomography (CT) finding of hyperdensity within the sella (n = 17, 48.5%, p = 0.02) and sellar Hounsfield units (mean 45 versus 38.1, p=0.05). Sellar HU were higher in the hemorrhagic pituitary apoplexy cohort. Similarly, hyperintensity on magnetic resonance imaging was more indicative of patients with hemorrhagic apoplexy according to T1 (p = 0.004), T2 (p = 0.004), and FLAIR (p = 0.04) imaging sequences. No difference was found in patterns of enhancement (p = 0.69) or restriction based on diffusion-weighted imaging (p = 0.54). Gradient echo (n=4) and susceptibility weighted imaging (n=1), while not performed in all patients, demonstrated hemorrhage within a pituitary adenoma in patients where this technique was used.

Conclusions: Our study did not demonstrate a unifying imaging feature in non-hemorrhagic apoplexy cases. Hemorrhagic apoplexy was more likely associated with hyperdensity on CT and hyperintensity on T1, T2 and FLAIR MRI sequences. Because of the variation of imaging findings in hemorrhagic and especially non-hemorrhagic apoplexy, imaging appearance inconsistent with hemorrhage should not be used to exclude the diagnosis of apoplexy.

Keywords: Apoplexy; pituitary; radiographic; imaging findings.

1. INTRODUCTION

Pituitary apoplexy was first described in the late nineteenth century but the clinical syndrome was not fully characterized in the literature until the mid-twentieth century [1,2]. It remains a relatively rare clinical entity and reliable diagnosis can be challenging. The clinical syndrome of pituitary apoplexy is related to mass effect and pituitary insufficiency secondary to hemorrhage or infarction of a pituitary tumor [1]. While many physicians are aware that apoplexy can be caused by hemorrhage, non-hemorrhagic apoplexy may be less familiar and the radiologic appearance may mimic that of a typical pituitary adenoma. This may cause a delay in diagnosis, or worse, an inaccurate diagnosis. The clinical presentations are variable but can include headache, nausea, vomiting, visual disturbances, symptoms of pituitary hormone insufficiency, and even death [1,2,3,4]. The endocrinologic ramifications of apoplexy are great as acute adrenal insufficiency from deficient secretion of adrenocorticotropic hormone (ACTH) can result in clinically significant and potentially fatal hemodynamic compromise [1].

The syndrome may not be initially recognized due to variable clinical presentations and findings on imaging studies making diagnosing pituitary apoplexy potentially difficult. Computed Tomography (CT) and magnetic resonance imaging (MRI) may provide additional information to assist with diagnosis. Recognizing associated imaging findings on multiple modalities will increase the likelihood of a timely diagnosis and appropriate management for this potentially fatal condition. Although CT scans are the modality of choice in many emergency rooms, they do not reliably detect hemorrhage in pituitary apoplexy and should not be used to exclude a diagnosis [4]. Furthermore, CT findings in non-hemorrhagic apoplexy with infarct alone have not been objectively characterized. MR offers several advantages, including improved detection of hemorrhage, and may be a superior tool for evaluating potential apoplexy [4]. Additionally, recent studies have demonstrated that MRI is a superior imaging modality to utilize in patients with non-hemorrhagic pituitary apoplexy secondary to infarction [1].

Aggressive clinical management with hydration and steroid replacement and prompt surgical decompression are the mainstays of treatment in pituitary apoplexy [1,3]. Early diagnosis allows for timely initiation of clinical and surgical management. At present, the diagnosis is predominantly clinical and relies upon the history and physical exam. Defining objective imaging criteria may facilitate early diagnosis and improved patient management. Additionally, the associated pathophysiology (hemorrhage, infarction, or hemorrhagic-infarction) may play a role in predicting clinical course and outcomes. Imaging findings may allow determination of underlying pathophysiology which may become valuable for clinical decision-making, e.g. timing of surgical decompression if a relationship between pathophysiology and likely clinical course becomes better defined. Our study aims to define imaging features that correlate with pathology findings in patients with pituitary apoplexy. These findings will add to the existing body of knowledge on the subject and provide physicians with additional objective tools for establishing an accurate diagnosis to optimize patient care.
2. MATERIALS AND METHODS

2.1 Study Sample

A total of three hundred eleven subjects consecutively admitted to a single institution with a diagnosis of pituitary tumor from January 2006 to February 2013 were included for initial analysis. Medical records for each subject were reviewed for clinical or imaging evidence of apoplexy. The initial diagnosis of apoplexy was based on clinical history, physical exam and initial laboratory workup. Thirty-seven patients who underwent surgical decompression for a clinical diagnosis of apoplexy were identified for inclusion in this study. Classification of hemorrhagic versus non-hemorrhagic was based on intra-operative observation and tissue pathology. Twenty patients were found to have evidence of hemorrhagic apoplexy and seventeen patients were classified as non-hemorrhagic.

Demographic data (Table 1) and medical co-morbidities (Table 2) were compared between the two groups. Patients with hemorrhagic apoplexy were found to be older and have a higher rate of hypertension. Imaging findings based on the report of an independent neuro-radiologist, intra-operative findings as reported in the operative report and documented pathology results.

2.2 Study Design

This was a retrospective cross sectional review of imaging findings in patients diagnosed with a known pituitary tumor who presented with pituitary apoplexy. Imaging findings using magnetic resonance imaging and computed tomography were reviewed and compared with pathology reports in thirty-seven subjects who underwent surgical decompression.

2.3 Data Analysis

A cohort statistical analysis was performed comparing hemorrhagic versus non-hemorrhagic apoplexy using Chi Square, Fisher exact test, logistic regression, ANOVA, and t-test. Hemorrhagic apoplexy was defined by evidence of hemorrhage on histopathology and intra-operative findings consistent with hemorrhage. Non-hemorrhagic apoplexy was defined by both absence of gross hemorrhage on operative findings and of hemosiderin on pathology.

The two groups were compared for the following imaging findings in the sellar region: Hyperdensity on Computed Tomography (CT), hyperintensity on Magnetic Resonance Imaging (MRI) sequences, enhancement patterns, and restriction on diffusion weighted MR sequences. Additionally a small subset of patients underwent......

| Table 1. Demographic data |
|---------------------------|
|                           | Hemorrhagic | Non-hemorrhagic | p value |
| **Age, mean ± SD**        | 52.2±15.1   | 42.5±14.2       | 0.05    |
| **Sex, n (%)**            |             |                 | 0.8     |
| Male                      | 11 (29.3)   | 10 (27.03)      |
| Female                    | 9 (24.3)    | 7 (18.9)        |
| **Race, n (%)**           |             |                 | 0.43    |
| White                     | 9 (24.3)    | 8 (21.6)        |
| Black                     | 11 (29.7)   | 8 (21.6)        |
| Hispanic                  | 0 (0.0)     | 1 (2.7)         |

| Table 2. Medical co-morbidities |
|------------------------------|
|                             | Hemorrhagic | Non-hemorrhagic | p value |
| Hypertension, n (%)         | 15 (40.5)   | 6 (16.2)        | 0.01    |
| Diabetes, n (%)             | 6 (16.2)    | 4 (10.8)        | 0.6     |
| Smoking, n (%)              | 6 (16.6)    | 5 (13.8)        | 0.9     |
| Peripartum, n (%)           | 1 (2.7)     | 1 (2.7)         | 0.9     |
| **BMI, mean ± SD**          | 33.3±13.6   | 32.5±10.8       | 0.84    |
gradient echo and susceptibility weighted imaging. Slice thickness on CT was 5 mm per institutional standards.

3. RESULTS AND DISCUSSION

3.1 Results

Imaging findings were analyzed in twenty hemorrhagic and seventeen non-hemorrhagic cases of pituitary apoplexy. Imaging analysis demonstrated a statistically significant difference in the hemorrhagic cohort’s Computed Tomography (CT) finding of hyperdensity within the sella (n = 20 versus n= 7, 48.5%; p = 0.02) and sellar Hounsfield units (HU) (mean 45 versus 38.1; p=0.05) (Figs. 1 and 2). Similarly, hyperintensity on magnetic resonance imaging was more indicative of patients with hemorrhagic apoplexy according to T1 (n=13 versus n=4; p = 0.004) (Fig. 2), T2 (n=12 versus n=5; p = 0.004) (Fig. 3), and FLAIR (n=13 versus n=6; p = 0.04) (Figs. 3-5) imaging sequences. No difference was found in patterns of enhancement (capsule, homogenous, or mottled; p = 0.69) (Fig. 6) or restriction based on diffusion-weighted imaging (p = 0.54). Additionally, Gradient echo (n=4) and susceptibility weighted imaging (n=1) demonstrated hemorrhage though these studies were only used on a small subset of patients.

3.2 Discussion

Pituitary apoplexy remains a largely clinical diagnosis that poses challenges due to the variability of clinical presentations. Objective tools that solidify the diagnosis would be valuable adjuncts for ensuring a timely diagnosis and optimal patient management, in particularly in patients with non-hemorrhagic apoplexy when the clinical diagnosis is unclear. Descriptions of the imaging features of pituitary apoplexy in the current literature are limited and the nomenclature can be confusing. Our study of imaging findings in patients with hemorrhagic and non-hemorrhagic pituitary apoplexy aims to better define imaging findings in both entities.
CT scans are readily available and are commonly used during the initial evaluation of patients with suspected apoplexy. Hemorrhage in the sella turcica may be seen as hyperdensity on non-contrast CT within 3 days of ictus [1]. As expected, sellar hyperdensity on non-contrast CT was observed in 90% of subjects with hemorrhagic apoplexy but also in 41% of subjects with non-hemorrhagic apoplexy. CT allows for the quantification of radiodensity by using the Hounsfield scale. Sellar HU were higher in the hemorrhagic pituitary apoplexy cohort. However, the finding of sellar hyperdensity on non-contrast CT imaging is non-specific and can also be observed in a variety of clinical entities including parasellar aneurysms, calcifications, mucoid cystic component of Rathke cleft cysts, pituitary cysts, craniopharyngioma cysts, and angiolipomas [5,6]. Additionally, in our experience many incidentally found pituitary macroadenomas appear hyperdense. The results of our study are consistent with prior studies that reported CT scans to have low sensitivity for diagnosing apoplexy and should not be solely used to exclude the diagnosis [1].

Semple et al. [3] in a multicenter study, demonstrated the correlation between histopathology and MR findings in patients treated for pituitary apoplexy. They separated patients into two distinct clinical entities based on the presence of hemorrhagic or non-hemorrhagic apoplexy [3]. MR findings consistent with infarct were described by Semple et al. [3] as rim enhancement and the absence of any imaging signs of hemorrhage. In their series, MR findings consistent with infarct were present in 94% of intraoperative reports and 88% of histopathological findings confirming pituitary infarct. Findings of this study were reported as similar to prior studies by the same group who suggest the subset of patients with infarct alone have a less severe clinical course with more gradual onset of symptoms and improved outcomes compared to apoplexy associated with hemorrhage [1,3].

In our study, rim enhancement was observed in 17% of the non-hemorrhagic cohort and 46% of the hemorrhagic cohort which is not consistent with the findings reported in other studies. Analysis of homogenous and heterogeneous patterns of enhancement also failed to demonstrate any statistically significant difference on patterns of enhancement in either the hemorrhagic or non-hemorrhagic cohort in our study. In our study, hyperintensity on T1, T2, and FLAIR sequences on MR were more commonly seen in the hemorrhagic cohort. The gradient echo and susceptibility weighted imaging techniques available on modern MR imaging may allow for improved visualization of hemorrhage and hemosiderin. Susceptibility and diffusion imaging may be limited by artifact at the skull base and consequently we do not feel that obtaining this technique on a small number of patients significantly impacts our findings. MR findings consistent with sellar hemorrhage were observed in 3 patients who did not have sellar hyperdensity on CT scan. An additional 2 subjects with hemorrhagic apoplexy and T1, T2 and FLAIR hyperintensities on MRI did not have CT imaging available for comparison. Based on our findings, both CT and MR imaging were useful tools for recognizing apoplexy and sensitivity is increased when both modalities are available.
Although our findings did not support earlier studies that suggest ring enhancement as an imaging finding in non-hemorrhagic apoplexy, identifying this subpopulation may be possible with MRI. Ring enhancement may be an associated finding with pituitary apoplexy and our small sample size may have limited our ability to demonstrate a significant association. In addition to the studies reported by Semple et al. [3], Nawar et al. [1] describe rim enhancement with an isointense or slightly hypointense appearance of the central gland/tumor. This finding is also reported as one of the diagnostic criteria of imaging apoplexy. Lee et al. [7] showed a positive correlation between imaging diagnosis and acute clinical presentation.

Another reported MR imaging finding in the literature is thickening of the sphenoid sinus mucosa [1,8]. Arita et al. [8] first described this finding in acute pituitary apoplexy. They propose several contributing mechanisms, including venous congestion, an inflammatory response and water-electrolyte imbalance secondary to posterior pituitary dysfunction. Liu and Couldwell [2] also reported this finding in their experience with pituitary apoplexy. In their retrospective review, they suggest a correlation between this finding with a more severe clinical course and worse outcomes. They used MR imaging to aid in the diagnosis of apoplexy and report detecting hemorrhage or infarct in all patients, but do not describe specific findings. We did not evaluate for the presence of sphenoid sinus mucosal thickening in our present study but this might be interesting to evaluate in future investigations. Anecdotally, this seems to be a more common finding with delayed presentation.

The major limitation of this study is the small sample size. This limitation is difficult to overcome given the low prevalence of pituitary apoplexy and the sample size in this study was comparable to sample sizes in other published literature on the subject. Additionally, gradient echo and susceptibility weighted images were not routinely obtained for sellar focused MRIs. These sequences are a potentially effective tool, especially if non-hemorrhagic cases actually have micro-hemorrhage detectable by these images when T1 findings are not consistent with hemorrhage.

An unexpected finding was the number of patients presenting with non-hemorrhagic apoplexy. Although not considered the traditional underlying pathophysiology in pituitary apoplexy, this group represented 46% of the patient population seen at our institution. This illustrates the critical importance of recognizing this subpopulation when clinically evaluating patients for possible apoplexy. Based on our findings we believe the clinical diagnosis can be aided with imaging imaging. Importantly, due to lack of a single characteristic MRI feature seen in non-hemorrhagic apoplexy, imaging cannot be used alone to exclude apoplexy from the differential diagnosis.

However, imaging findings are an important clinical adjunct for diagnosis and provide important data for pre-operative planning. MRI can help define the relationship of surrounding anatomy and vasculature, identify significantly compression of the optic apparatus and assess for cavernous sinus involvement [1] while CT can provide information about bony anatomy. The two imaging modalities are complementary and provide greater knowledge when used in combination. The authors of this study recommend obtaining both a CT scan and MR imaging including T1 with and without contrast, T2, GRE, FLAIR, DWI and ADC sequences in patients suspected of pituitary apoplexy. Future studies are needed to further delineate imaging findings in both hemorrhagic and non-hemorrhagic subsets of pituitary apoplexy. Future studies to evaluate the reliability of gradient echo sequences and susceptibility weighted images in identifying non-hemorrhagic apoplexy are also warranted.

4. CONCLUSION

The diagnosis of pituitary apoplexy remains largely clinical and should be considered with any patient that presents with acute visual changes, cranial nerve deficits, laboratory values consistent with hypopituitarism and a pituitary adenoma. Although the clinical presentation and physical exam remain the most important elements in diagnosing apoplexy, imaging provides useful information for medical decision-making, operative planning, and prognosis in both patients with hemorrhagic and non-hemorrhagic pituitary apoplexy. In the present study we attempted to quantify the imaging features of apoplectic patients to aid clinicians in both making a diagnoses and to further standardize the nomenclature for hemorrhagic and non-hemorrhagic pituitary apoplexy.

Early identification of hemorrhagic and non-hemorrhagic pituitary apoplexy may be improved
by understanding of the common imaging findings associated with each entity. Our study did not demonstrate a unifying imaging feature in non-hemorrhagic apoplexy cases. Hemorrhagic apoplexy was more likely associated with hyperdensity on CT and hyperintensity on T1, T2 and FLAIR MRI sequences. Because of the variation of imaging findings in hemorrhagic and especially non-hemorrhagic apoplexy, imaging appearance inconsistent with hemorrhage should not be used to exclude the diagnosis of apoplexy.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The Institutional Review Board of the University of Alabama at Birmingham provided approval prior to the conduct of this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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