Radiological Apoplexy and Its Correlation with Acute Clinical Presentation, Angiogenesis and Tumor Microvascular Density in Pituitary Adenomas

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Objective: Pituitary apoplexy is life-threatening clinical syndrome caused by the rapid enlargement of a pituitary tumor due to hemorrhage and/or infarction. The pathogenesis of pituitary apoplexy is not completely understood. We analyzed the magnetic resonance imaging (MRI) of pituitary tumors and subsequently correlated the radiological findings with the clinical presentation. Additionally, immunohistochemistry was also performed to determine whether certain biomarkers are related to radiological apoplexy.

Methods: Thirty-four cases of pituitary adenoma were enrolled for retrospective analysis. In this study, the radiological apoplexy was defined as cases where hemorrhage, infarction or cysts were identified on MRI. Acute clinical presentation was defined as the presence of any of the following symptoms: severe sudden onset headache, decreased visual acuity and/or visual field deficit, and acute mental status changes. Angiogenesis was quantified by immunohistochemical expression of fetal liver kinase 1 (Flk-1), neuropilin (NRP) and vascular endothelial growth factor (VEGF) expression, while microvascular density (MVD) was assessed using Endoglin and CD31.

Results: Clinically, fourteen patients presented with acute symptoms and 20 for mild or none clinical symptoms. Radiologically, fifteen patients met the criteria for radiological apoplexy. Of the fifteen patients with radiologic apoplexy, 9 patients presented acute symptoms whereas of the 19 patient without radiologic apoplexy, 5 patients presented acute symptoms. Of the five biomarkers tracked, only VEGF was found to be positively correlated with both radiological and nonradiological apoplexy.

Conclusion: While pituitary apoplexy is currently defined in cases where clinical symptoms can be histologically confirmed, we contend that cases of radiologically identified pituitary hemorhages that present with mild or no symptoms should be designated subacute or subclinical apoplexy. VEGF is believed to have a positive correlation with pituitary hemorrhage. Considering the high rate of symptomatic or asymptomatic pituitary tumor hemorrhage, additional studies are needed to detect predictors of the pituitary hemorrhage.

Key Words: Pituitary adenoma · Pituitary apoplexy · Pituitary hemorrhage · Angiogenesis · Microvascular density · VEGF.
mor compresses the vascular supply, resulting in ischemia and necrosis of both the anterior pituitary gland and tumor. Likewise, a second theory contends that the critical perfusion pressure of pituitary adenomas lies below normal arterial pressures, and sudden alterations in perfusion pressure predispose the adenoma to infarction. A third theory postulates that as the tumor enlarges, it simply outgrows its original blood supply, resulting in ischemic necrosis and secondary hemorrhage\(^\text{30}\).

Angiogenesis is the result of an extremely complex biological mechanism in which several growth factors cooperate to stimulate vascular proliferation\(^\text{3,40}\). While angiogenesis is crucial for tumor growth, development and sometimes correlates with metastases, prognosis and survival, its role in endocrine tumors has not been fully elucidated\(^\text{11,15}\). Generally, benign neoplasms are sparsely vascularized, with the existing vessels possessing a fragile and abnormal morphology. Along these lines, pituitary tumors are typically less vascular than the normal pituitary tissue\(^\text{30}\).

Vascular endothelial growth factor (VEGF) is an intercellular signaling protein present in vascular endothelial cells which plays a pivotal role in angiogenic promotion, stimulating cellular proliferation, migration, and increased vascular permeability\(^\text{41,15}\). Mechanistically, the biological activities of VEGF are primarily mediated by 2 unique tyrosine-kinase receptors: VEGFR2 [or fetal liver kinase 1/kinase insert domain-containing receptor (Flk-1/KDR)] and VEGFR1 [or flms-like tyrosine kinase (Flt-1)]. Research results now suggest that these two receptors play different roles in angiogenesis and signal transduction pathways, with Flk-1/KDR (VEGFR2) now believed to specifically bind VEGF on vascular endothelial cells. Neuregulin (NRP) 1 - another previously identified neuronal receptor that mediates repulsive growth cone guidance - has also been recently shown in vitro to function in endothelial cells as an isoform-specific VEGF receptor as well as VEGF receptor 2 coreceptor. Accordingly, the angiogenic factors VEGF, Flk-1 and NRP-1 were selected here for angiogenesis evaluation\(^\text{20}\).

In general, most solid neoplasms are characterized by a high microvascular density (MVD), a property essential for tumor growth and metastasis\(^\text{13}\). In contrast, pituitary adenomas are significantly less vascular than normal pituitary gland tissue, suggesting that angiogenic inhibitors may play a role in the pathologic processes associated with these lesions\(^\text{26,29,30}\). In prior studies, MVD has been assessed by a technique of counting vessels labeled with various antibodies specific to different vascular endothelial markers, including endoglin (CD105) and CD31 (platelet endothelial cell adhesion molecule), both of which have different sensitivities for endothelium detection. To date, the exact relationship between angiogenesis, MVD, tumor bleeding and infarction, and the clinical behavior of pituitary adenomas has not been well characterized. Here, we examined the pituitary tumor bleeding and infarction using MRI imaging and evaluated its correlation with both clinical presentation and the degree of angiogenesis or MVD.

**MATERIALS AND METHODS**

**Patients and methods**

In total, 34 subjects with pituitary tumors were enrolled for the current study, all of whom underwent surgery between 2005 and 2009 (Table 1). Of these, were 18 males (mean age=52 years) and 16 were females (mean age=50.6 years). The medical records of these subjects were additionally reviewed to identify acute clinical presentations.

**Radiological & clinical assessment**

**Radiological assessment**

All subjects underwent a 3T MRI with intravenous administration of Gd-DTPA (0.1 mmol/kg), producing essential T1, T1-weighted and T2-weighted images. On MRI, infarctions showed no hemorrhage on T1- or T2-weighted imaging sequences, and no enhancement was seen after gadolinium administration except some characteristic rim or capsule enhancement\(^\text{20}\). T2-weighted imaging is the most sensitive sequence for the detection of intracranial hemorrhage, however changes need to be identified on different MRI sequences in order to date the hemorrhage. In the first 1-2 days, intraparenchymal hemorrhages appear hyperintense on T1-weighted images and hypointense on T2-weighted images. Between days 3 through 15, hemorrhages appear bright on both T1 and T2-weighted images due to degradation of hemoglobin into methemoglobin. After day 15, fluid levels within hemorrhages may develop as a result of the sedimentation of the exsanguinated blood\(^\text{30}\). Regardless of apoplexy symptoms, cases of hemorrhage, necrosis or cysts detected on MRI were defined as radiological apoplexy\(^\text{30}\). Tumor size was defined as maximum tumor diameter on preoperative MRI imaging and evaluated its correlation with both clinical presentation and the degree of angiogenesis or MVD.

Table 1. Demographic features of 34 patients with pituitary adenomas

| Characteristic          | No. of patients | %   |
|-------------------------|-----------------|-----|
| No. of patients         | 34              |     |
| Sex                     |                 |     |
| Male                    | 18              | 53  |
| Female                  | 16              | 47  |
| Age                     |                 |     |
| 20-30                   | 3               | 9   |
| 31-40                   | 3               | 9   |
| 41-50                   | 6               | 18  |
| 51-60                   | 14              | 41  |
| 61-70                   | 7               | 21  |
| 71-80                   | 1               | 3   |
| Symptoms                |                 |     |
| Acute*                  | 14              | 41  |
| Mild or none            | 20              | 59  |

\*Acute: sudden onset severe headaches, nausea and/or vomiting, visual disturbances, mental status changes, and/or cases of sudden onset ophthalmoplegia.
Clinical apoplexy and non-radiological apoplexy. Demographic factors, such as mean age, tumor size, presence of angiogenic factors and MVD, were then compared between groups.

Clinical assessment
Each subject was evaluated for overall clinical presentation. Acute clinical presentation was defined as the presence of any of the following symptoms: sudden onset of headache, severe nausea and vomiting, visual disturbance, altered level of consciousness or the sudden onset of extraocular movement limitations.

Immunohistochemical parameters

Angiogenesis (VEGF, Flk-1, NRP-1)
All markers were stained in the cytoplasm and then observed in a 400-magnification field of view. VEGF was quantified by the percentage of stained tumor cells, which were further characterized on a continuous scale ranging from weakly positive (1+) to strongly positive (2+). The immunostaining score was calculated by multiplying the percentage of labeled cells by the intensity of the staining (range, 1+=1-100, 2+=101-300). Flk-1 and NRP-1 were both interpreted as either negative or positive, as determined by the presence of the stained cells among the vascular endothelial cells.

Microvascular densities (Endoglin, CD31)
To quantify MVD by immunohistochemistry for endoglin and CD31, the three most high density areas (“hot spot” areas) were selected for each sample. Vessel numbers were then measured ×200 (×20 objective lens and ×10 ocular lens; 0.82 mm² per field) in order to calculate the average value. In the current study, microvascular endothelial cells were defined as microvessels, and large muscular vessels were excluded. Vascular densities were assessed by three separate examiners, all of whom were blinded to the tumor type and size, with the final result comprising the average number of blood vessels identified by each observer.

Immunohistochemical staining techniques
Paraffin embedded tissue for each patient was first sectioned at thicknesses of 4-5 μm. Slides were then deparaffinized in xylené (3 times for 5 minutes each) and subjected to three sequential 5-minute treatments in solutions of 90%, 75%, and 50% ethanol. The slides were then rinsed in distilled water for 5 minutes. Next, to recover antigenicity (antigen retrieval technique), the slides were soaked in a citrate buffer (0.01 M, pH 6.0), heated in a microwave oven, cooled in cold PBS (phosphate buffer saline), and lastly treated with a 0.5% hydrogen peroxide-methanol solution for 10 minutes in order to suppress endogenous peroxidase in the sliced tissue. After another rinsing in distilled water, the slides were stained with auto-immune stainer using following monoclonal antibodies: endoglin (Novocastra; Newcastle-upon-Tyne, UK), CD31 (Dako Cytomation; Glostrup, Denmark), and VEGF, Flk-1, NRP-1 (Santa Cruz Biotechnology; Santa Cruz, CA, USA) as the primary antibodies. The slides were then allowed to react with the secondary antibody solution (containing biotinylated anti-mouse immunoglobulin antibodies) for 10 minutes at room temperature, before undergoing 3 sequential rounds of rinsing, each lasting 3 minutes, with Tris buffer. After the streptavidin peroxidase detection system was used to induce biotin-avidin specific binding, the slides were rinsed again with Tris buffer, treated for 10 minutes with 3,3′-diaminobenzidine tetrahydrochloride for antibody color staining. A final round of contrast staining was then visualized with Mayer’s hematoxylin.

Statistics analysis
All data were processed and analyzed using SPSS software (V. 12.0; SPSS Inc., Chicago, IL, USA). Continuous variables were analyzed by independent t-test and categorical variables by crosstab analysis. Statistical significance was defined as $p<0.05$.

RESULTS

Correlation of radiological apoplexy and acute clinical presentation
Acute clinical presentation was identified in 14 patients, 9 subjects of them met the criteria for radiological apoplexy (Fig. 1A), while 5 patients did not show an evidence of radiological apoplexy. Of the 20 cases presented with mild or no clinical symptoms, 6 patients met the criteria for radiological apoplexy.
Notably, tumor sizes were larger among individuals with radiological apoplexy, however this difference did not reach statistical significance.

Radiological apoplexy and angiogenesis

Among individuals with evidence of radiological apoplexy, 8 were found to be weakly VEGF positive, while 7 were strongly positive for VEGF. In the group without radiological apoplexy, 16 subjects were weakly positive for VEGF and 3 strongly positive (Fig. 3). These data indicate a significantly higher rate of VEGF positivity in the radiological apoplexy group \( (p=0.045) \). Both Flk-1 and NRP were also categorized into positive and negative responses, with 8 cases found to be Flk-1-positive in the radiological apoplexy group and 13 in the non-radiological apoplexy group \( (p=0.384) \). Conversely, 5 cases were NRP-positive in the radiological apoplexy group, while 9 were NRP-positive in the non-radiological apoplexy group \( (p=0.424) \) (Table 3).

Radiological apoplexy and microvascular density

The mean CD31 and Endoglin levels were 51.2±21.3 and 53.4±17.2 in the radiological apoplexy group, and 53.79±19.6 and 52.63±21.8 in the non-radiological apoplexy group \( (p=0.716; p=0.904) \) (Table 4). No significant differences in either Endoglin or CD 31 were observed between groups.

Relationship between angiogenesis and microvascular density

A positive correlation was observed between angiogenesis and MVD. The mean CD31 level was 59.00±17.9 in the Flk-1-posi-
pituitary apoplexy or subclinical pituitary apoplexy, with diag-

Table 4. Microvascular density markers and pituitary apoplexy

|                         | No. of patients | Endoglin (mean microvessel number) | CD31 (mean microvessel number) |
|-------------------------|----------------|-----------------------------------|--------------------------------|
| Radiological apoplexy   | 15             | 53.4                              | 51.2                           |
| No radiological apoplexy| 19             | 52.6                              | 53.7                           |
| p value                 | 0.904          | 0.716                             |                                |

Table 5. Correlation between markers of angiogenesis and microvascular density

| Flk-1 (-)                | 13             | 45.69±23.9                        | 42.38±19.9                     |
| Flk-1 (+)                | 21             | 57.52±15.3                        | 59.00±17.9                     |
| p value                  | 0.088          | 0.017                             |                                |
| NRP (-)                  | 20             | 44.10±18.1                        | 44.80±20.5                     |
| NRP (+)                  | 14             | 65.71±14.1                        | 63.86±13.6                     |
| p value                  | 0.001          | 0.005                             |                                |
| VEGF (+)                 | 24             | 46.46±18.0                        | 47.71±18.7                     |
| VEGF (+++)               | 10             | 68.70±13.7                        | 64.50±19.1                     |
| p value                  | 0.001          | 0.024                             |                                |

DISCUSSION

Pituitary apoplexy occurs when an existing pituitary adenoma undergoes acute hemorrhage and/or infarction. The resulting accumulation of blood and edema produces a sudden increase in contents of the sella turcica, which subsequently compresses surrounding vessels and other local structures. Clinically, this process often results in acute severe headaches, visual disturbances or complete loss of vision, ophthalmoplegia, mental status changes and hypopituitarism. Most epidemiologic studies suggest that the incidence of pituitary tumor apoplexy is less than 5% (with estimates ranging from 0.6 to 10%), as it occurs in 2% of all surgically resected adenomas.

Notably, the definition of pituitary apoplexy has not been consistent throughout the literature. Mohr and Hardy, in a review of 664 patients with pituitary adenomas, reported that, while 64 (9.6%) were found to have features of hemorrhage or necrosis intraoperatively, only 4 (0.6%) clearly experienced clinical features consistent with pituitary apoplexy. Conversely, Wakai et al. used a broader definition of pituitary apoplexy that included all tumors showing evidence of hemorrhage or bloody fluid during surgery, and accordingly reported an incidence of 16.6% in a series of 560 patients with pituitary tumors. In their study of 12 pituitary adenoma patients with intratumoral evidence of hemorrhage identified on computed tomographic scan or MRI, Ostrov et al. only found 3 with clinical signs of pituitary apoplexy. Several other reports exist describing asymptomatic pituitary tumor hemorrhages, with asymptomatic hemorrhage or infarction observed in 14 to 22% of all pituitary tumors, while clinical apoplexy occurring in only 0.6 to 9%.

These asymptomatic hemorrhages are typically small, but at times have been more extensive. Traditionally, such cases of asymptomatic pituitary hemorrhage or infarction have been dubbed subacute pituitary apoplexy or subclinical pituitary apoplexy, with diagnosis often delayed or missed in these cases. In our study, pituitary hemorrhage and/or infarction occurred in 15/34 cases (44.1%), while both acute clinical presentation and radiological apoplexy was observed in 9/34 (26.4%). Consequently, subclinical apoplexy was diagnosed in 6/34 subjects (17.6%). Although positive correlation between radiological apoplexy and acute clinical presentation was found statistically, we should consider that significant number of patients with pituitary adenomas suffer pituitary hemorrhage without definite clinical apoplexy symptoms. We included pituitary cysts in the definition of radiological apoplexy, as these lesions often represent radiological evidence of previous hemorrhages. This is the reason why the incidence of apoplexy was high in our study.

Most evidence in the literature suggests that all types of human pituitary adenomas secrete quantifiable levels of VEGF, a signaling protein known to induce vascularization under both physiological and pathological conditions and needed to maintain existing vascular structures. VEGF is also an important regulator of endothelial cell layer permeability. In pituitary adenomas, the clinical significance of VEGF expression is somewhat controversial. In their study of 39 patients with pituitary adenomas, Arita et al. reported a positive relationship between intratumoral hemorrhage and VEGF expression. As all cases were VEGF positive in our study, we stratified VEGF expression into weakly and strongly positive, and subsequently identifying a positive correlation with pituitary hemorrhage rates. We believe that the increased vascular permeability induced by VEGF overexpression may result in fluid exudation and cyst formation, a process which may ultimately increase tissue pressure in adenomas. Pituitary adenomas are reportedly irrigated at least partially through the pituitary portal system. Thus, even a small increase in tissue pressure within adenomas may suffice to overwhelm the inherently low perfusion pressure and result in tumor tissue necrosis and consequent intratumoral hemorrhage.

The effects of VEGF on vessel integrity and permeability in...
normal human pituitary tissue seem to be mediated primarily through Flk-1 and its co-receptor NRP-1, both of which are expressed in vessel endothelial cells. Here, we confirmed previous reports that pituitary adenomas are less well vascularized than normal pituitary tissue. However, in one previous study including over 100 human pituitary tumors, McCabe et al. described a significant over-expression of Flk-1 mRNA (average 14-fold, maximum 233-fold) identified by quantitative PCR. In this same study, the authors also report increased Flk-1 protein expression (quantified by Western blot) in several of the adenoma cases. Strong upregulation of the VEGF/VEGF receptor system has previously been reported in several types of rapidly growing and densely vascular solid tumors. Since human pituitary adenomas exhibit a completely different pathophysiology, a significant over-expression of Flk-1 would be unexpected in these slowly growing and poorly vascularized tumors. Nevertheless, the discrepant findings regarding Flk-1 expression in human adenomas should be clarified in future studies. In our study, correlations between Flk-1, NRP and pituitary hemorrhage were not statistically significant.

Tumor microvascular density is often used a proxy measurement for angiogenesis, and can be quantified by vessel counts. In such cases, vessels are typically identified by positive immunostaining, using antibodies to varying vascular endothelial markers, including as Factor VIII-related antigen, CD31, CD34 antigen, and Ulex europaeus agglutinin. Such studies have subsequently shown that pituitary adenomas have a significantly lower vascular density when compared to nontumorous adenohypophysis. This relative dearth of blood vessels seen in pituitary adenomas stands in marked contrast to most other tumors. Neoplasms of the lung, breast, and prostate, all are significantly more vascular than their nontumorous parent tissues. This lack of significant angiogenesis may, therefore, contribute to the slow pace of growth characteristic of most pituitary tumors and explain the relative rarity of metastases. Furthermore, the ultrastructural alterations seen in the endothelial cells of such adenomas may also result from hypoxia deriving from an inadequate blood supply to the tumor. Further researches are needed on the problem why the hemorrhage happens more frequently in adenoma, in which the vascularity is lower than the normal gland. It is unlikely to be difficult to explain the hemorrhage tendency with only the actual VEGF because we didn’t compare the VEGF expression of normal pituitary gland to pituitary adenoma directly. Probably it could be related not with angiogenesis itself but with permeability or pressure relationship with surrounding structures, or there may be other factors in addition to VEGF.

However, such correlations between pituitary hemorrhage and pro-angiogenic factors or MVD were not clearly identified by our data.

CONCLUSION

Although pituitary apoplexy is currently defined as clinical symptoms that can be histologically confirmed, many reports designated the cases without acute symptoms. Therefore, a further definition is necessary to distinguish such cases, so-called subacute or subclinical apoplexy. VEGF was found to have positive correlation with the pituitary hemorrhage and positive correlation was also identified between angiogenesis and MVD. Considering the high rate of symptomatic or asymptomatic pituitary tumor hemorrhage, additional studies are needed to detect predictors of the pituitary hemorrhage.

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Radiological Apoplexy and Its Correlation with Angiogenesis in Pituitary Adenomas  

JS Lee, et al.

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