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Apparent diffusion coefficient and pituitary macroadenomas: pre-operative assessment of tumor atypia

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Abstract

Rationale and objectives Pituitary macroadenomas are predominantly benign intracranial neoplasms that can be locally aggressive with invasion of adjacent structures. Biomarkers of aggressive behavior have been identified in the pathology literature, including the proliferative marker MIB-1. In the radiology literature, diffusion weighted imaging and low ADC values provide similar markers of aggressive behavior in brain tumors. The purpose of this study was to determine if there is a correlation between ADC and MIB-1 in pituitary macroadenomas.

Materials and methods A retrospective review of diffusion imaging and immunohistochemical characteristics of pituitary macroadenomas was performed. The ADC ratio and specimen Ki-67 (MIB-1) indices were measured. Linear regression analysis of normalized ADC values and MIB-1 indices was used to compare these parameters.

Results There were 17 patients with available ADC maps and MIB-1 indices. Local invasion was confirmed by imaging and intraoperative visualization in 11 patients. The mean ADC ratio for the invasive group was 0.68, with a mean MIB-1 index of 2.21 %. In the noninvasive group, the mean ADC ratio was 1.05, with a mean MIB-1 index of 0.9 %. Linear regression analysis of normalized ADC values versus MIB-1 demonstrates a negative correlation, with a linear slope significantly different from zero ($p = 0.003$, correlation coefficient of 0.77, and r squared = 0.59).

Conclusion We determine a strong correlation of low ADC values and MIB-1, demonstrating the potential of diffusion imaging as a possible biomarker for atypical, proliferative adenomas, which may ultimately affect the surgical approach and postoperative management.

Keywords Pituitary adenoma · Magnetic resonance imaging · Diffusion weighted imaging · Proliferation index (MIB-1)

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Introduction

Pituitary adenomas are relatively common intracranial neoplasms primarily found in adults during the 3rd to 6th decades [1–3]. Although generally considered benign, these tumors exhibit a wide range of biological behavior in terms of hormonal activity and proliferative capacity [1]. Pituitary adenomas are classified by three major criteria: anatomic features, including size and presence of local invasion into adjacent structures; function, whether the lesion is hormonally active; and histology, which includes

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underlying immunohistochemical characterization [4, 5]. Our study focused on non-functional adenomas, specifically adenomas that were not hormonally active. More recently, presence of some molecular and immunohistochemical markers were associated with more aggressive and hormonally inactive atypical adenomas [6]. Pituitary carcinomas, as opposed to atypical pituitary adenomas, are defined by distant cerebrospinal fluid and or systemic metastasis, and are exceptionally rare lesions that account for less than 1 % of all primary pituitary tumors [6, 7]. Atypical adenomas demonstrate an intermediary behavior between nonaggressive benign adenomas and rare pituitary carcinomas, indicating a potential for recurrence rates higher than typical adenomas [6, 8].

Markers of cell proliferation, such as the immunohistochemical detection of Ki-67 antigen have been suggested as biomarkers for aggressive behavior in atypical pituitary adenomas [3, 9, 10]. Ki-67 is a nuclear antigen expressed in proliferating cells identified by monoclonal antibody MIB-1 [10]. The role of MIB-1 as a proliferation marker is well established in the pathology literature, and numerous studies have investigated the potential of MIB-1 labeling index in identifying more aggressive tumors, including meningiomas and gliomas [11, 12]. Although there is no well established threshold for proliferative markers such as MIB-1 immunohistochemistry, prior studies demonstrated higher MIB-1 indices in recurrent adenomas, suggesting a potential for MIB-1 labeling index as a biomarker for more aggressive, atypical adenomas [10, 13].

In the neuroradiology literature, DWI is a well-established sequence for the evaluation of intracranial neoplasms. Specifically, the ADC value is often correlated with tumor cellularity and tumor grade [14]. Furthermore, multiple prior studies have demonstrated the role of DWI in the evaluation of pituitary adenomas, ranging from preoperative assessment of tumor consistency to correlation of ADC with the proliferative marker MIB-1 [14–18].

The purpose of this study was to evaluate the role of DWI in the characterization of pituitary macroadenomas in order to establish imaging biomarkers of more aggressive tumors beyond what is identified on anatomic imaging. In order to do that, we first compared ADC and MIB-1 indices of invasive and noninvasive adenomas. Furthermore, we tested the hypothesis that there is an inverse relationship between ADC and MIB-1 labeling index, with lower ADC values of pituitary macroadenomas correlating with higher MIB-1 labeling index. In establishing a negative correlation between ADC and MIB-1, we hypothesize that ADC values, specifically lower ADC values can be used to suggest the presence of more aggressive, proliferative tumors not otherwise identified on conventional MR sequences.

Materials and methods

Patients

We have searched our institution's Department of Radiology PACS for patients with pituitary adenomas who underwent MRI evaluation between 2003 and 2013. We obtained the appropriate permission for the study from the Institutional Review Board. We excluded patients from the initial search results based on the following exclusion criteria: patients without available preoperative DWI/ADC sequence; DWI/ADC containing motion or dental hardware artifact; adenomas measuring\ 2 cm; adenomas that were composed of large cysts and or hemorrhage, or calcifications as identified by anatomic imaging were all excluded from the study.

Pathology

Ki-67 immunohistochemical stains were performed on 5-micron thick whole slide sections from formalin-fixed paraffin-embedded tissue on charged slides using standard methods (MIB-1 rabbit monoclonal antibody, Ventana Medical Systems, Tucson, AZ, USA). MIB-1 labeling indices were calculated by a single observer as percentage of tumor nuclei labeling with clone MIB-1. In each case, the area with the highest number of positive tumor nuclei was selected for counting on a representative slide and at least 200 cells were counted.

Imaging

All MRI examinations were performed using 1.5-T and 3-T clinical scanners. ADC maps were calculated from diffusion-weighted images using b values of 0 and 1000 s/mm^2. Diffusion-weighted imaging was performed using 5-mm section thickness with 1-mm spacing, a field of view of 24 cm, and a matrix size of 128 9 128.

Round regions of interest (ROIs) measuring 0.4–0.7 cm^2 were drawn by a single investigator to measure the intratumoral ADC values. The investigator is a board-certified neuroradiology Clinical Instructor, working under close supervision of a fellowship-trained neuroradiologist with a Certificate of Additional Qualification in Neuroradiology with more than 10 years of experience in Neuroradiology. Areas containing cyst and large vessels were avoided.

Round ROIs with similar size were also drawn over the normal white matter in the ipsilateral centrum semiovale to calculate normalized tumor to white matter ADC ratios.

Statistical analysis

The normalized ADC ratios of invasive and noninvasive pituitary adenomas were compared using the nonparametric Mann–Whitney test, without assumption of a Gaussian distribution of the data. MIB-1 labeling indices of invasive and noninvasive pituitary adenomas were also compared using a Mann–Whitney test (GraphPad Instat, GraphPad Software).

An inverse function was applied to the normalized ADC ratios in order to perform linear correlation analysis of normalized ADC as a function of MIB-1 labeling index. Linear correlation analysis was performed using the Pearson product moment correlation (GraphPad Instat, GraphPad Software).

Results

A search of the Radiology department PACS yielded a total of 138 cases of pituitary adenomas. Among these, 30 patients were identified with preoperative MRI imaging containing DWI/ADC. Thirteen additional patients were further excluded based on our specific exclusion criteria as detailed in the methods section, including 4 containing artifact on the DWI sequence; 3 with lesions measuring \ 2 cm; and 6 containing large cystic and hemorrhagic components. A total of 17 patients were included in the study with the following demographics: 10 males and 7 females; age range of 35–75 years (mean age 54 years).

Pathology

Of the 17 cases of pituitary adenomas, 15 of the tumors demonstrated negative immunohistochemical stains for ACTH, GH, and prolactin; two of the adenomas demonstrated positive stains for prolactin and GH respectively. Summary of correlation of ADC values, MIB-1 labeling indices and local invasion is presented in Table 1.

Imaging

Local invasion of adjacent structures, including the cavernous sinus, was determined by MRI evaluation and confirmed by intraoperative visualization. Invasion was defined as tumor visualized in the medial margin of the cavernous sinus and or within the adjacent structures to the sella, confirmed by MR imaging and intraoperative visualization. Invasion was further classified as per the Knosp grading scale and Table 2 summarizes the Knosp scores, ADC ratio, and MIB-1 index for all 17 patients [19]. Overall, the adenomas with local invasion demonstrated statistically significant lower normalized ADC values as compared to the non-invasive counterparts, with a mean of 0.68 as compared to 1.05 in non-invasive adenomas ($p = 0.0057$). Additionally the MIB-1 indices were statistically higher in the adenomas with local invasion, with a mean of 2.21 % as compared to 0.90 % in non-invasive adenomas ($p = 0.0287$).

There was an inverse relationship between normalized ADC values and MIB-1 (Fig. 1). A nonlinear transformation of the normalized ADC values was performed by applying an inverse function (reciprocal of the value) in order to perform linear regression. There is a statistically significant correlation between normalized ADC values and MIB-1 indices, with a p value of 0.003, a correlation coefficient of 0.77, and r squared of 0.59 (Fig. 2).

Immediate post-operative imaging and follow up for the 17 patients revealed 6 patients with gross total resection of their adenomas with the remaining patients categorized as subtotal resection. Of the 17 patients, only 2 had progressive disease after resection and radiation therapy, both of which had subtotal resections and had low ADC ratios (0.61, 0.64) with higher MIB-1 indices (2.0 respectively).

Discussion

Pituitary adenomas, the majority of which are histologically benign, can exhibit a wide range of behavior, and preoperatively predicting more aggressive adenomas remains a challenge. Often in the literature, the term “aggressive” has been used synonymously with “invasive” in

Table 1 Summary of ADC values, MIB-1 indices and local invasion

Pituitary tumor type	Number of tumors	ADC range	Mean ADC	Median ADC	MIB-1 index range	Mean MiB-1	Median MIB-1
Invasive	11	0.49–1.4	0.68	0.64	0.78–5	2.2	2.00
Non-invasive	6	0.8–1.6	1.05	0.96	0–1.44	0.9	1.00

Table 2 Summary of ADC values, MIB-1 indices and Knosp grading

Invasion	ADC ratio	MIB-1 index	Knosp score
Yes	0.58	2	4
Yes	0.49	5	4
Yes	0.67	2	3
Yes	0.53	4	3
Yes	0.61	2	4
Yes	0.64	2	3
Yes	1.4	0.78	3
Yes	0.71	2	3
Yes	0.64	1	3
Yes	0.57	0.8	4
Yes	0.66	2.7	2
No	0.97	0.86	3
No	0.88	1.44	2
No	1.1	0.59	2
No	0.8	1.13	0
No	1.6	0	1
No	0.95	1.4	1

the evaluation of pituitary adenomas [9]. Invasive pituitary adenomas that exhibit relatively higher mitotic activity, MIB-1 labeling index of [3 %, and excessive p53 immuno-reactivity are classified as atypical adenomas by the World Health Organization [6, 9]. Furthermore, these atypical adenomas have been associated with higher risk of recurrence or lack of therapeutic response [9, 10, 13].

Our study found a statistically significant difference in the proliferation marker MIB-1 as well as the ADC values in invasive pituitary adenomas as compared to noninvasive pituitary adenomas. We also determined an inverse relationship between normalized ADC values and MIB-1 labeling indices, with higher levels of MIB-1 correlating with lower ADC values. This finding suggests the potential of ADC as a radiologic marker for atypical adenomas not identified on conventional MRI sequences, in order to predict the likelihood of recurrence.

As with other intracranial neoplasms, understanding and establishing the cellularity and proliferative potential of these adenomas is essential to the preoperative assessment of the tumors for appropriate surgical resection and postoperative management. Conventional anatomic imaging, although helpful in establishing the extent of tumor and invasion of adjacent structures, does not allow for the assessment of tumor atypia. Advanced imaging techniques including DWI have been utilized for the assessment of tumor behavior, demonstrating a correlation between lower ADC values and higher grade, cellular tumors [14]. The application of DWI for the evaluation of pituitary adenomas however, is limited. Prior studies evaluating the role of ADC in the assessment of adenoma consistency for preoperative evaluation are conflicting [16–18]. Furthermore, there is minimal literature available regarding the use of

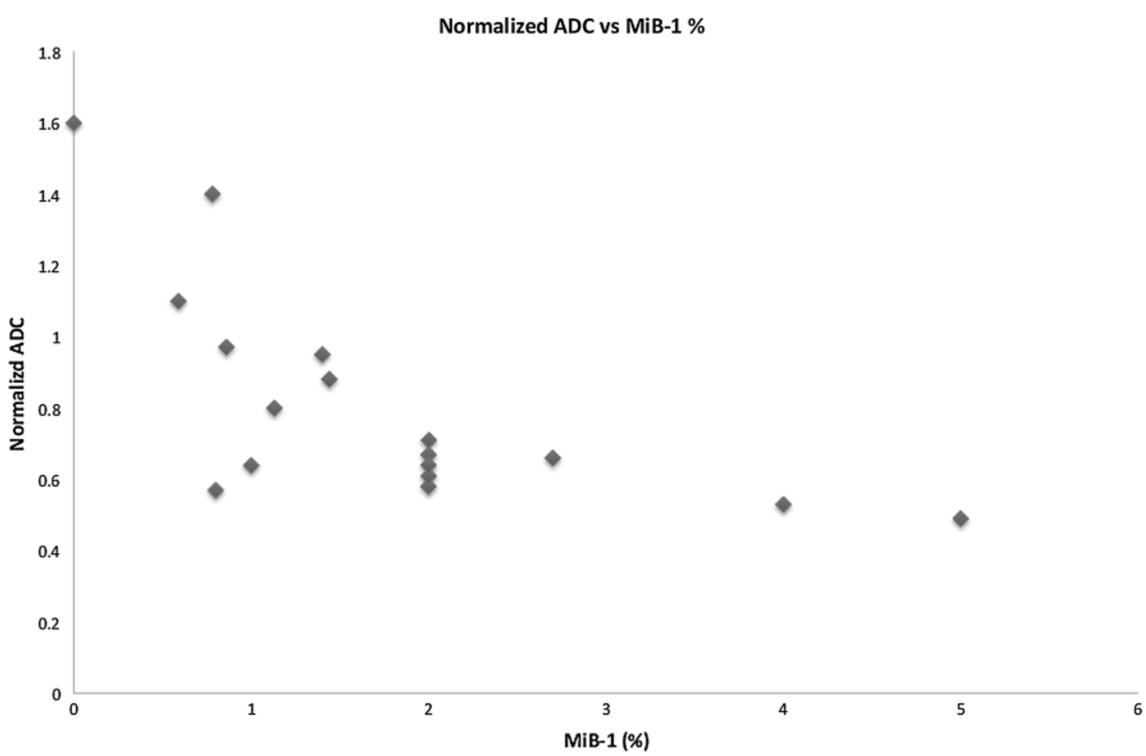

Fig. 1 Plot of normalized ADC values versus MIB-1 percentage demonstrates an inverse association between these parameters

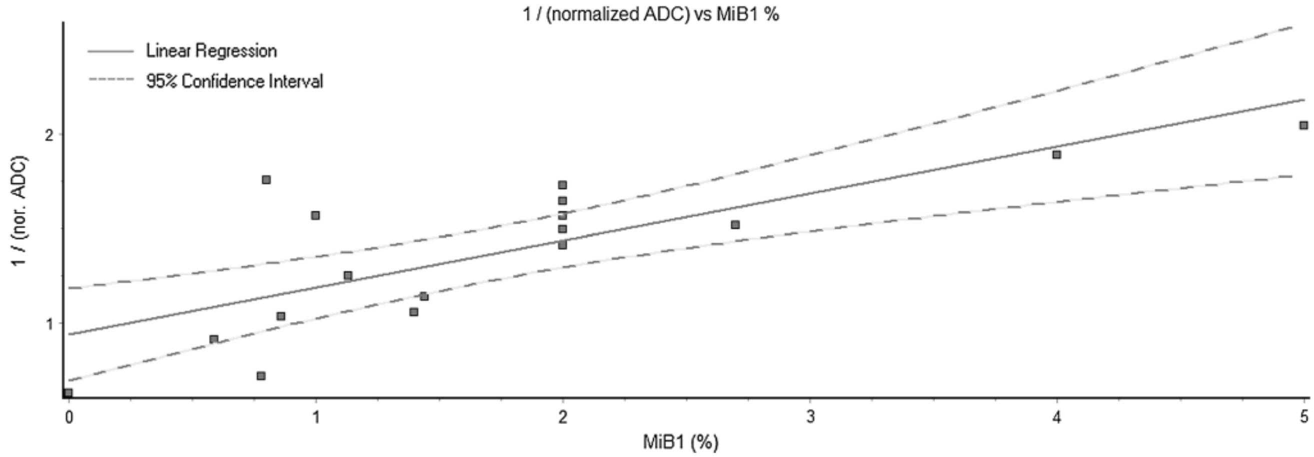

Fig. 2 Plot of linearized normalized ADC value versus MIB-1 percentage. An inverse function is applied to the normalized ADC values in order to perform linear regression analysis. The linear regression line and 95 % CI are shown, demonstrating a statistically significant correlation between these parameters (p value = 0.003). Correlation coefficient of the linear regression = 0.77, with r^2 = 0.59

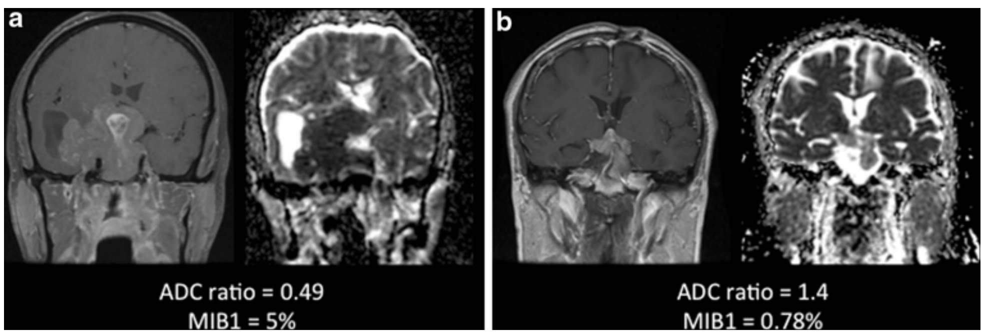

Fig. 3 Apparent diffusion coefficient (ADC) maps and T1 post contrast MR images of invasive pituitary macroadenomas (a, b). The ADC values differentiate the two invasive adenomas, with low ADC values seen in (a) correlating with higher MIB-1 index, suggesting a more atypical invasive adenoma

ADC for assessment of pituitary adenoma behavior and classification.

The use of ADC in this study further helped delineate a subgroup of adenomas not identified on conventional MRI sequences. Prior studies suggested the classification of adenomas as noninvasive, invasive, and aggressive-invasive and our results demonstrate a similar classification pattern [9]. With the use of ADC, there is further differentiation of invasive adenomas into two separate categories reflecting more aggressive behavior and atypical features as identified by lower normalized ADC ratios (Fig. 3).

The limitation of the study is the small sample size. DWI is not routinely performed for MRI evaluation of the sella at most practices, including our institution; therefore ADC analysis was not possible for the majority of pituitary adenomas imaged during the evaluated timeframe. As the clinical utility of DWI for pituitary ademonas becomes more evident, future studies may not have similar shortcomings, as pituitary protocols are more commonly performed with DWI. Correlation of DWI values with clinical outcomes such as tumor recurrence should also be investigated in larger studies. Despite the small sample size, our findings provide preliminary results that indicate a negative correlation between ADC and MIB-1, and larger studies are needed to further establish the role of DWI in these commonly occurring neoplasms.

Conclusion

Despite a small sample size, we found a negative correlation between ADC values and MIB-1 labeling indices in pituitary adenomas, identifying diffusion imaging as a potential biomarker for atypical adenomas. DWI and ADC values should be evaluated prospectively to identify potentially more aggressive, atypical adenomas, which may have a higher likelihood for recurrence.

Compliance with ethical standards

Conflict of interest The authors of this manuscript have no conflicts of interest.

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