Detection of MRI-negative Cushing’s disease by FLAIR imaging: is it reliable?

TO THE EDITOR: We read with great interest the article by Chatain et al. (Chatain GP, Patronas N, Smirniotopoulos JG, et al: Potential utility of FLAIR in MRI-negative Cushing’s disease. J Neurosurg [epub ahead of print October 13, 2017. DOI: 10.3171/2017.4.JNS17234]). In this article, the authors evaluated the diagnostic utility of FLAIR imaging in the detection of microadenomas in patients with Cushing’s disease (CD). All 23 patients (24 pituitary adenomas) underwent volumetric gradient recalled echo (3D-GRE) MRI and FLAIR scanning preoperatively. Compared with intraoperative findings and postoperative histopathology, 3D-GRE sequences correctly confirmed 18 location-concordant tumors and were unable to identify 4 tumors (MRI-negative CD). In contrast, FLAIR sequences only correctly confirmed 12 tumors (noted incorrectly as 13 in the abstract) and were unable to identify 10 tumors. In the past decade, many researchers have explored the usefulness of FLAIR imaging in brain tumors, while few highlighted the significance of it in the diagnosis of pituitary adenomas. Exactly as the data showed in this study, compared with that of 3D-GRE MRI, the accuracy of FLAIR in detecting CD microadenomas was much lower, which means the diagnostic value of FLAIR imaging is very limited.

Chatain et al. also found all 5 patients with negative 3D-GRE MRI displayed FLAIR hyperintensity. Among them, 4 patients had location-concurrent positive histopathological findings, and in 1 patient (case 7) the concordance of imaging with histopathology was unable to be identified because the foci of FLAIR hyperintensity was not removed during surgery. The authors concluded that FLAIR helps 3D-GRE determine MRI-negative CD for surgical planning, which we think is quite debatable. The standalone specificity of 3D-GRE and FLAIR in this study was equal, but is impossible in real life. Considering the innate instability of specificity/sensitivity as well as the rather small sample size of this study, statistical errors undoubtedly existed. In addition, the positive and negative likelihood ratios (more statistically stable than specificity/sensitivity) of 3D-GRE were 1.64 and 0.36, while those of FLAIR were 1.1 and 0.9. This indicates that the possibility of confirming the foci of FLAIR hyperintensity as tumors was just 52.4%.

Even though the authors used T2-weighted sequences to screen for cysts within the pituitary gland or the adenoma, it is still difficult to differentiate. As for the localization, small Rathke cleft cysts (RCCs) usually lie within the central posterior aspect of the anterior lobe adjacent to the posterior lobe, similar to CD microadenomas. The signals of cysts on MR images are diverse due to their different compositions of cystic fluid. When protein components are in the majority, RCCs will present T2 signal hypo-/isointensity, precontrast FLAIR isointensity, and postcontrast FLAIR hyperintensity, which are similar to the radiological appearances of microadenomas. When MRI-negative microadenomas and hyperintense cysts on FLAIR coexist in the same pituitary gland, the authors may regard the cysts as tumors and then select incorrect surgical sites. In conclusion, we can use FLAIR as an auxiliary sequence in CD, but the diagnostic value of it cannot be overestimated. Further studies with a similar design are needed.

Approximately 120 patients with CD underwent surgery annually at Peking Union Medical College Hospital, which is one of the largest pituitary centers in China. Generally, T1-weighted gadolinium-enhanced MRI as well as dynamic gadolinium-enhanced MRI (routine MR sequences) are used to detect and localize about 90% of CD adenomas. The concordance of lateralization by MRI was 80% compared with surgical findings and histopathological results. In addition, the departments of neurosurgery, endocrinology, and radiology of our medical center are cooperating to explore the diagnostic utility of the (18)F-FDG and (68)Ga DOTA-TATE dual-tracer PET/MRI in CD microadenomas. The preliminary research indicates that dual-tracer PET/MRI can detect an additional 10% of the routine MRI-negative and location-concordant microadenomas.

We sincerely hope that the investigators (neurosurgeons, endocrinologists, and radiologists) of our center can collaborate with Dr. Chatain and colleagues to explore more efficient radiological examinations of MRI-negative CD microadenomas.

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References

Disclosures
The authors report no conflict of interest.

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Although it has been suggested that preoperative visualization of microadenomas in CD may not improve surgical outcomes, negative preoperative imaging causes enough consternation among clinicians that it leads to adjunct imaging or extensive reviews of clinical experience. In MRI-negative cases, distinct adenomas are identified less commonly, leading to a more extensive exploration of the pituitary gland. In this setting, we attempted to improve the detection of microadenomas by applying the principle of retained contrast within microadenomas. Modern MRI techniques rely on delayed contrast wash-in to detect microadenomas as hypointense lesions. We wondered whether delayed FLAIR imaging could lead to detection of microadenomas due to retained contrast. We discovered in the current study that the standalone sensitivity of pituitary FLAIR imaging in detecting microadenomas remains poorer than best anatomical imaging (3D-GRE). However, an analysis of MRI-negative instances did reveal the potential utility of FLAIR as a complementary tool to 3D-GRE. We do not propose replacing 3D-GRE or dynamic pituitary imaging with FLAIR given the low sensitivity (55%) and fair interrater agreement (κ = 0.32). In MRI-negative cases, if a microadenoma is not immediately observed upon surgical exposure, surgeons are forced to perform extensive surgical exploration of the sella. In light of the ineffectiveness of hemihypophysectomy guided by inferior petrosal sinus sampling lateralization, we hope that pituitary FLAIR provides a starting point for surgeons to initiate surgical exploration. We agree with Drs. Wang and Xing that further studies are needed to clearly establish the role of FLAIR in the detection of microadenomas in CD. We have also been exploring other means to improve detection of microadenomas in CD including intraoperative MRI and FDG PET imaging. We acknowledge the gracious offer that Dr. Xing has made for a collaborative effort, and we will reach out to make this a reality.

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