

WHAT DOES FLUMAZENIL PET ADD TO AN EVALUATION FOR TEMPORAL LOBECTOMY?

Periventricular White Matter Flumazenil Binding and Postoperative Outcome in Hippocampal Sclerosis

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PURPOSE: In patients with hippocampal sclerosis (HS), anterior temporal lobe resection offers the possibility of a long-lasting suppression of seizures in two-thirds of patients. White matter (WM) [^{11}C]flumazenil volume of distribution (FMZ- V_d) reflects the number of neuronal cell bodies in WM. Our objective was to correlate WM FMZ- V_d in patients with unilateral HS and postsurgical outcome.

METHODS: We performed [^{11}C]flumazenil positron emission tomography ([^{11}C]FMZ-PET) in 15 patients with refractory mesial temporal lobe epilepsy (mTLE) and a quantitative MRI diagnosis of unilateral HS subsequently histologically verified in all cases. Median follow-up was 7 years (range, 6–9 years). Metabolite-corrected arterial plasma input functions and spectral analysis were used to generate

parametric images of [^{11}C]FMZ- V_d . Statistical parametric mapping (SPM99) with explicit masking was used to investigate the entire brain volume including WM.

RESULTS: Eight patients had Engel class IA outcome (completely seizure-free since surgery), and seven were not seizure-free. Comparison of seizure-free patients with those who continued to have seizures after surgery revealed areas of increased FMZ binding around the posterior horns of the ipsilateral ($z = 3.7$) and contralateral ($z = 2.7$) ventricles in those with suboptimal outcomes.

CONCLUSIONS: Preoperative [^{11}C]FMZ-PET can detect periventricular increases of WM FMZ binding, implying heterotopic neurons in WM, in patients with mTLE. The presence of such increases correlates with a poorer outcome.

COMMENTARY

[^{11}C]flumazenil positron emission tomography ([^{11}C]FMZ-PET) was used for the evaluation of patients with presumed mesial temporal lobe epilepsy (mTLE) as early as 1988, showing decreased benzodiazepine receptor binding in temporal lobe foci (1). It has not become part of routine preoperative evaluation, which is due to technical difficulties as well as the proliferation of other, particularly MRI-based, imaging procedures. Some investigators have suggested that [^{11}C]FMZ-PET can detect reduced benzodiazepine receptor binding that predicts surgical outcome in 30–40% of MRI-negative patients with suspected mesial temporal epilepsy, but its role seems limited when MRI shows mesial temporal sclerosis (2). Hammers et al. now suggest, however, that detection of increased periventricular white matter (WM) FMZ binding may be an adverse prognostic factor, even when MRI shows mesial temporal sclerosis (3).

Using statistical parametric mapping (SPM99) and an effect threshold of 2.5 standard deviations, Hammers and colleagues reported that group comparison showed increased periventricular WM FMZ binding in non-seizure-free, com-

pared with seizure-free, patients. On individual analysis, four of seven patients who were not seizure-free after temporal lobectomy versus three of eight who did become seizure-free demonstrated increased periventricular WM binding (compared with control values) around the posterior horns of both ventricles ipsilateral and contralateral to the epileptic focus, with some individual variations. Patients who were not seizure-free or those with increased FMZ binding tended to be less likely to have strictly unilateral discharges on video-EEG. It was interesting that 3 of 13 controls, compared with a separate group of 12 controls, also had increased periventricular FMZ binding, when the same statistical threshold was used. The authors suggest that FMZ-PET is detecting occult periventricular migration abnormalities, or microdysgenesis, and that these malformations may underlie additional seizure foci, leading to persistent postoperative seizures.

A previous study from the same group showed a correlation between FMZ binding in temporal lobe WM and neuron number in patients who had anterior temporal lobectomy (3). In their earlier study, however, using a somewhat different voxel of interest-based analysis method, both increases and decreases of FMZ binding were found outside the epileptic focus and involved neocortical regions in addition to the posterior periventricular WM detected in this new study. Even if increased FMZ binding does prove to be associated reliably with ectopic

neurons, the significance of decreased binding outside the putative epileptogenic zone will still have to be explained. Since these decreases were present in cortex rather than WM, they could be associated with neuronal loss. However, in patients with mesial temporal sclerosis, reduced binding for both benzodiazepine- and 5HT_{1A}-receptor PET ligands has been shown not to be caused purely by neuronal loss (4,5). Alterations in receptor binding reflect functional as well as structural changes.

Moreover, PET results may reflect fluctuating neuronal activity as well as the location of a “stable” epileptogenic zone. Previous 2-deoxy-2-[¹⁸F]fluoro-d-glucose (FDG) PET studies have suggested that the type of seizure occurring most recently before a PET scan influences the extent of hypometabolism and that return to baseline activity may be prolonged (6,7). Another recent FMZ-PET study showed binding variations that could lead to clinically significant changes in interpretation in 5 of 10 patients who had two scans, 1 week apart (8). Hippocampal binding was reduced in patients with shorter intervals between their last seizure and the scan. Variation between scans in lateralization on visual analysis, although not in quantitative asymmetry index, was seen in several patients.

Hammers et al. point out that the difference in the proportion of patients with increased periventricular FMZ binding between seizure-free and non-seizure-free was small and that detection of increased binding cannot be used to predict temporal lobectomy outcome. A much larger number of patients would be needed to confirm their results. However, their study demonstrates the potential for neuroimaging eventually to lead to a more careful, noninvasive selection of patients for epilepsy surgery, with improved outcome and reduced risk.

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References

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