Current Literature
In Clinical Science

Blurring the Lines Between Lesional and Nonlesional MRI

Blurring in Patients With Temporal Lobe Epilepsy: Clinical, High-field Imaging and Ultrastructural Study.

Garbelli R, Milesi G, Medici V, Villani F, Didato G, Deleo F, D'Incerti L, Morbin M, Mazzoleni G, Giovagnoli AR, Parente A, Zucca I, Mastropietro A, Spreafico R. *Brain* 2012;135(pt 8):2337–2349.

Magnetic resonance imaging-positive temporal lobe atrophy with temporo-polar grey/white matter abnormalities (usually called 'blurring') has been frequently reported in patients with temporal lobe epilepsy associated with hippocampal sclerosis. The poor distinction of grey and white matter has been attributed to various causes, including developmental cortical abnormalities, gliosis, myelin alterations, a non-specific increase in temporal lobe water content and metabolic/perfusion alterations. However, there is still no consensus regarding the genesis of these abnormalities and no histopathological proof for a structural nature of magnetic resonance imaging changes. The aim of this study was to investigate the pathological substrate of temporo-polar blurring using different methodological approaches and evaluate the possible clinical significance of the abnormalities. The study involved 32 consecutive patients with medically intractable temporal lobe epilepsy and hippocampal sclerosis who underwent surgery after a comprehensive electroclinical and imaging evaluation. They were divided into two groups on the basis of the presence/absence of temporo-polar blurring. Surgical specimens were examined neuropathologically, and selected samples from both groups underwent high-field 7 T magnetic resonance imaging and ultrastructural studies. At the clinical level, the two groups were significantly different in terms of age at epilepsy onset (earlier in the patients with blurring) and epilepsy duration (longer in the patients with blurring). Blurring was also associated with lower neuropsychological test scores, with a significant relationship to abstract reasoning. On 7 T magnetic resonance image examination, the borders between the grey and white matter were clear in all of the samples, but only those with blurring showed a dishomogeneous signal in the white matter, with patchy areas of hyperintensity mainly in the depth of the white matter. Sections from the patients with blurring that were processed for myelin staining revealed dishomogeneous staining of the white matter, which was confirmed by analyses of the corresponding semi-thin sections. Ultrastructural examinations revealed the presence of axonal degeneration and a significant reduction in the number of axons in the patients with blurring; there were no vascular alterations in either group. These data obtained using different methodological approaches provide robust evidence that temporo-polar blurring is caused by the degeneration of fibre bundles and suggest slowly evolving chronic degeneration with the redistribution of the remaining fibres. The article also discusses the correlations between the morphological findings and clinical data.

Commentary

Important developments in the MRI evaluation of patients with medically resistant focal epilepsy are frequently reviewed in this journal. In the current review, we again turn to MRI and highlight a recent article examining the pathological substrate of MRI "white matter blurring" in the temporal pole of patients with mesial temporal sclerosis (MTS). The MRI abnormalities in patients with MTS, an early epilepsy imaging success story, extend well beyond the hippocampus. In addition to hippocampal atrophy and increased T_2-weighted signal, subsequent studies showed differential atrophy with the hippocampal head most affected, along with entorhinal, perirhinal, and amygdala atrophy (1). Not only the hippocampal and cortical gray matter are abnormal in patients with MTS (2, 3), but there are also MRI abnormalities in the temporal pole white matter (4) and even outside the temporal lobe, with subcortical and extratemporal atrophy (5). The diffuse MRI abnormalities are consistent with the spectrum of neuropathological findings affecting neocorticies, including widespread, laminar-specific neocortical abnormalities (6) and white matter pathology (4, 6, 7).

White-matter "blurring" refers to the increased signal on T_2-weighted images in white matter and the gray/white-matter junction. Garbelli et al. point out that while the underlying pathology for the increased T_2-weighted signal and poor distinction of gray/white matter has been variably attributed to diffuse gliosis, heterotopic gray matter in the white matter, myelin alterations, nonspecific increase in temporal lobe water content, and metabolic/perfusion alterations (4, 7, 8, 9), there is no consensus regarding the underlying functional or histologic abnormalities. Diffuse gliosis was not found in a previous

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pathological study (10). Given the lack of definite histopathology, the aim of Garbelli et al. was to investigate the pathological substrate of temporo-polar blurring.

Garbelli et al. investigated 32 consecutive patients with medically intractable temporal lobe epilepsy and evidence of MTS on 1.5T MRI. Patients with dual pathology were excluded. On the basis of 1.5T MRI, the patients were catagorized into two groups: group 1 patients had MTS with blurring within the ipsilateral temporal pole white matter, and group 2 patients had MTS without blurring. All patients ultimately underwent an anterior temporal lobectomy. The surgical tissue underwent neuropathological analysis, high-field ex vivo 7T MRI, and ultrastructural studies.

The 1.5T FLAIR and T_2-weighted images of all of the patients in group 1 showed increased signal in the temporal pole white matter, with blurring of the gray/white-matter junction ipsilateral to the MTS. In 72% of group-1 patients, there was also ipsilateral temporal pole atrophy. In group 2, the T_2-weighted signal intensity was homogenous and normal throughout the temporal pole white matter, and the gray/white-matter interface was clearly distinct. The two groups of patients were different in terms of age at onset and duration of epilepsy. Group-1 patients (i.e., patients with blurring, increased T2-weighted signal intensity, and indistinct gray/white-matter junction) had onset of epilepsy at a younger age and longer duration of epilepsy.

Of interest, ex vivo 7T magnetic resonance images of patients with and without blurring (groups 1 and 2) had clear, distinct gray/white-matter boundaries. There were, however, patchy areas of hyperintense T_2 signal and lower fractional anisotropy in white matter samples taken from patients with blurring on 1.5T clinical scans (group 1). The increased T_2-weighted signal is nonspecific, but the decreased fractional anisotropy supports a loss of white-matter integrity and organization.

The histopathological studies demonstrated MTS in all cases and also found a variable degree of diffuse white-matter gliosis and CD68-positive cells. There was an excess of diffusely distributed heterotopic neurons in the white matter of all the surgical samples from both groups. Ultrastructural studies revealed heterogeneous Black-Gold staining for myelin in the white matter of group-1 samples, but homogeneous staining in group 2. The group-1 samples also had more extra-axonal space and fewer myelinated and unmyelinated fibers. These ultrastructural abnormalities are consistent with MRI findings showing decreased fractional anisotropy and evidence of increased extracellular water content in group-1 tissue.

These data provide evidence that blurring of the temporal pole white matter is caused by fiber bundle degeneration and white matter shrinkage. Given that group-1 patients had earlier age of onset and longer duration of epilepsy, the study further suggests a slowly evolving chronic degeneration with redistribution of remaining white matter fibers. From the clinical perspective, blurring was associated with lower neuropsychological test scores, but there was no difference in surgical outcomes. The study provides strong evidence that the commonly observed MRI "blurring," seen in over half of patients with TLE, is due to a loss of the number of white matter fibers and a reduced percentage of area occupied by myelinated axons. Further, while the etiology of the fiber loss is not known, there is no evidence for an inflammatory etiology. The data provide strong evidence that the white-matter blurring in the temporal pole of patients with MTS is caused by degeneration of fiber bundles and a slowly evolving chronic degeneration with the redistribution of the remaining fibers.

Whether the current findings apply more broadly to subtle abnormalities seen in patients without MTS, and in particular, TLE with normal MRI (11) is not known. If subtle gray-white matter blurring could provide an imaging signature to guide lateralization of normal MRI temporal lobe epilepsy and be prognostic for outcome, that would be significant. The use of ex-vivo tissue imaging at 7T represents a novel application of high-field imaging and is clinically relevant with the emergence of higher field imaging. The relevance of the current results to blurring of the gray/white junction seen in cortical dysplasia is unclear (12). The MTS cases considered here all had well-delineated cortical/white-matter junctions.

by Gregory A. Worrell, MD, PhD

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