

Diffusion Histograms in CADASIL

Hugues Chabriat, MD, PhD

See related article, pages 2559–2565

Diffusion MRI is a unique tool to investigate the microstructure of cerebral tissue. Diffusion-driven displacements of water molecules can probe the tissue architecture at a microscopic scale well beyond the usual image resolution.¹ Diffusion is a 3D process. In cerebral white matter, where the movements of water molecules are maximal along the bundles of axons, molecular mobility may be anisotropic. In acute ischemia, cytotoxic edema, which occurs after the failure of ATP-dependent ionic pumps at the cell membrane, is responsible for a reduction of the extracellular space and increased tortuosity. These structural alterations are presumably responsible for the major reduction in the random movements of water molecules (eg, diffusion) detected early after arterial occlusion. Conversely, beyond the acute phase of ischemia, MRI diffusion has been used to measure the loss of structural components responsible for the increase in movements of water molecules. Increased diffusion and loss of diffusion anisotropy have been detected not only inside the ischemic area but also in cerebral regions remote from the core infarct.²

Small vessel diseases (SVDs) are responsible for diffuse cerebral lesions located mostly in the subcortical gray and white matter in both hemispheres. These lesions are presumably caused by chronic ischemia and possibly by secondary degenerative processes. Diffusion tensor imaging studies previously showed an increase in diffusion and loss of anisotropy in hyperintense areas, as seen on T2-weighted images in various SVDs, particularly in hypertension-related SVDs,³ as well as in Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), a genetic model of SVD. Interestingly, in contrast to the extent of T2 hyperintensities, diffusion parameters were found strongly correlated with the mini mental state examination score, Rankin score, or intelligence quotient in small samples of subjects.^{3,4} In presence of diffusion modifications in multiple brain areas with normal or abnormal appearance on conventional MRI, we previously suggested to use diffusion histograms as a simple and global method to evaluate and represent diffusion values in CADASIL patients.^{3,5} Parameters derived from these histograms obtained in 16 patients were found to be strongly correlated with simple clinical scales. Most important, changes in the magnetic resonance diffusion values were detected after the follow-up of a small subgroup of patients. These results were promising and suggested

that such parameters may be used as surrogate markers in this disorder.⁵

In the study of Holtmannspotter et al in this issue of *Stroke*,⁶ the value of diffusion histogram parameters in the follow-up of CADASIL patients has been definitively confirmed. The authors measured T2 lesion volumes over the whole brain in association with mean diffusivity histograms in a fixed supraventricular section of both hemispheres in 62 CADASIL patients over a period of 26 months. They observed that T2 lesion volume- and diffusion-derived values were significantly modified over this period. They verified that these diffusion changes were not related to aging by using a control group. Most important, they found that diffusion changes over this period were strongly correlated with clinical worsening. This was not true for the variation of T2 lesion volume measured during the same period. These results further demonstrate that microstructural changes underlying ischemic T2 lesions are more clinically relevant than the extent of hyperintensities.

An important finding in the study is that diffusion measurement appears as the main predictor of clinical progression in CADASIL, which also confirms previous limited data. Therefore, the measurement of diffusion will possibly become one of the most important prognostic markers in CADASIL and may aid in stratification for future preventive trials.

Measurement of diffusion with MRI presents many advantages compared with parameters derived from conventional MRI. The whole brain can be assessed within few minutes, and the measures are relatively independent from the magnetic resonance scanner. Diffusion is also a physical measure independent from the MRI sequence. The results of Holtmannspotter et al suggest that this technique may be used in the future as a simple tool to assess the global tissue loss occurring in diffuse small vessel diseases of the brain. In CADASIL, the results support the use of diffusion histogram parameters as a complementary outcome measure in future therapeutic trials.

References

1. Le Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N, Chabriat H. Diffusion tensor imaging: concepts and applications. *J Magn Reson Imaging*. 2001;13:534–546.
2. Buffon F, Molko N, Herve D, Porcher R, Denghien I, Pappata S, Le Bihan D, Bousser MG, Chabriat H. Longitudinal diffusion changes in cerebral hemispheres after MCA infarcts. *J Cereb Blood Flow Metab*. 2005;25:641–650.
3. O'Sullivan M, Morris RG, Huckstep B, Jones DK, Williams SC, Markus HS. Diffusion tensor MRI correlates with executive dysfunction in patients with ischemic leukoencephalopathy. *J Neurol Neurosurg Psychiatry*. 2004;75:441–447.
4. Molko N, Pappata S, Mangin JF, Poupon C, Vahedi K, Jobert A, LeBihan D, Bousser MG, Chabriat H. Diffusion tensor imaging study of subcortical gray matter in CADASIL. *Stroke*. 2001;32:2049–2054.
5. Molko N, Pappata S, Mangin JF, Poupon F, LeBihan D, Bousser MG, Chabriat H. Monitoring disease progression in CADASIL with diffusion magnetic resonance imaging: a study with whole brain histogram analysis. *Stroke*. 2002;33:2902–2908.
6. Holtmannspotter M, Peters N, Opherk C, Martin D, Herzog J, Brückmann H, Sämann P, Gschwendtner A, Dichgans M. Diffusion MR histograms as a surrogate marker and predictor of disease. Progression in CADASIL: a two-year follow-up study. *Stroke*. 2005;36:2559–2565.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Department of Neurology, Hôpital Lariboisière, Université Paris 7, France.

Correspondence to Hugues Chabriat, MD, PhD, Department of Neurology, Hôpital Lariboisière, Université Paris 7, 2 rue Ambroise Paré, 75010 Paris, France. E-mail: hugues.chabriat@lrb.ap-hop-paris.fr

(*Stroke*. 2005;36:2526.)

© 2005 American Heart Association, Inc.

Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000000001.00000.00

KEY WORDS: CADASIL ■ diffusion ■ MRI