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maging in stroke continues to be one of the most dynamic fields of stroke research. Over the past year, researchers have used imaging for acute stroke diagnosis, treatment, and management; to assist in the evaluation of new therapies; to gain insight into neurorecovery, to investigate genetic links; and to better understand animal models of stroke. A full range of imaging technologies are being deployed in the fight against stroke: near-infrared optical, magnetic resonance, positron emission tomography (PET), ultrasound, and x-ray CT are all in active use, aided by both routine and novel tracers and contrast agents. A complete overview of all these advances is not possible in the space allotted here. Hopefully, the sampling of the advances over the past year provided here will convey some of the excitement and activity present in this field.

Imaging is often used to first diagnose both ischemic and hemorrhagic stroke, and advances continue to be made in these areas. The long-standing concept of the ischemic penumbra continues to be confirmed by PET, MRI, and CT. Two multicenter studies published in 2006 demonstrated the potential of imaging to identify candidate patients. In DEDAS,1 the MRI diffusion/perfusion mismatch identified patients in the 3- to 9-hour time window for treatment with the thrombolytic desmoteplase, with apparent benefit especially in patients who fulfilled all MRI criteria. In the DEFUSE study,2 MRI was used successfully to identify both patient subgroups likely to benefit and subgroups unlikely to benefit or possibly to be harmed from treatment in the 3- to 6-hour window. Both of these studies further encourage the notion that treatment might be able to be based not on the clock but rather tailored to an individual patient. Studies with CT methodology are also beginning to support this approach.3,4

Although the general concept of the diffusion-perfusion mismatch as an imaging marker for the ischemic penumbra seems supported, efforts continue to improve delineation of salvageable versus nonsalvageable tissue, versus patients who might be harmed by attempts at thrombolysis, all in hopes of better tailoring treatments to individual patients. This past year has seen substantial advances in these efforts, particularly with MRI and PET techniques. In addition to the clinical studies cited above, the comparison of diffusion/perfusion–weighted imaging (DWI-PWI) to quantitative imaging of flow and oxygen consumption by PET, which “shaped the concept underlying modern acute stroke imaging and remains the gold standard,” has been applied in several studies for validation of the DWI-PWI mismatch pattern on the PET-derived discrimination of irreversibly damaged, penumbra and hypoperfused tissue—in short, testing this notion not on a patient-level basis, where studies are showing general agreement, but on a voxel-by-voxel basis, where biological and individual heterogeneity is more identifiable. The notion that the DWI lesion contains the finally infarcted tissue with false-positive prediction of up to 25%,6,7 and that the mismatch overestimates the penumbra as defined by increased oxygen extraction fraction and extends into considerable areas with noncritical oligemia,8 was supported by further investigations: whereas the DWI lesion indicates impairment of energy metabolism, the change in apparent diffusion coefficient does not reliably predict tissue outcome,9 and the degree of disturbance in oxygen consumption was variable within individual DWI lesions suggesting variable outcome with potential for recovery.10 In contrast to DWI-PWI, early (<6 hours) hypoa attenuation on CT which is related to the severity of ischemia (PET) and the diffusion changes (DWI) both underestimat e the penumbra.11

Given these limitations at the tissue level, a number of approaches have been investigated with some success.12 C-flumazenil (FMZ) was shown to be a reliable early marker of preserved neuronal integrity with a correct prediction of 85% of cortical destruction volume and high specificity (negligible false positivity).12 In patients with chronic internal carotid occlusion, selective neuronal damage could be demonstrated by FMZ PET in the hemispheres of patients with border zone infarction beyond the regions of infarcts supporting the hemodynamic origin of these lesions.13 Selective loss of cortical neurons was also shown with iomazenil single-photon emission computed tomography (IMZ-SPECT) in patients with striatocapsular infarctions in transiently hypoperfused cortical tissue which was morphologically intact on MRI.14 These studies suggest that FMZ may prove to be a reliable tracer for neuronal integrity with higher specificity than DWI. The disadvantage—besides requiring PET equipment—is the short half life of the usual carbon-11 label. This can be overcome by using fluorine-18 label, which would allow FMZ to be a widely distributed radiotracer.15
One PET tracer for imaging hypoxia as a surrogate marker of the penumbra is 18F-fluoromisonidazole (FMISO). Binding of this tracer has been shown to occur in a peri-infarct distribution suggesting penumbra tissue, and some of the indicated tissue has been shown to progress to infarction, whereas some is salvaged.\textsuperscript{16,17} In an experimental study with temporary middle cerebral artery occlusion in rats, the validity of binding of this tracer to hypoxic tissue was documented confirming the value of FMISO for studying cellular hypoxia in ischemic stroke.\textsuperscript{18}

One MRI method for identifying hypoxia is the same BOLD imaging approach used for functional MRI studies. This oxygen-dependent MRI signal change appears to provide a metabolic indicator of tissue at risk in acute stroke patients,\textsuperscript{19} and may provide a superior means for identification of the penumbra. Additional techniques that are under active development include MRI-based pH imaging\textsuperscript{20} and microglial activation using PET. Microglial activation indicates the neuroinflammatory response to ischemic stroke and can be visualized by the specific ligand for peripheral benzodiazepine receptor sites \textsuperscript{\textsuperscript{11}C-PK11195.} Binding of the tracer rises considerably 72 hours after stroke in the core, the peri-infarct zone and even in the contralateral hemisphere suggesting progressing tissue damage.\textsuperscript{21,22} With the limited effect of available treatment, these delayed pathophysiological mechanisms may represent a therapeutic opportunity for ischemic stroke.

While there is an extensive amount of effort on imaging acute ischemic stroke, imaging has also been highly active in other areas. 2006 saw extensive work looking at the functional impact of stroke and stroke recovery. Crossed cerebellar diaschisis (CCD) has been a functional observation in supratentorial infarction\textsuperscript{23} and generally is considered a persistent phenomenon even despite clinical recovery. In a study of patients receiving IV thrombolysis,\textsuperscript{24} it was found that CCD occurs as early as 3 hours after stroke and might be reversible; acute CCD was closely related to the volume of supratentorial hypoperfusion, but at later time points CCD was disconnected from supratentorial perfusion but strongly associated to outcome measures; and CCD was not susceptible to non-nutritional reperfusion. As a consequence, CCD which has not been taken into account during the last few years may add valuable information to interpret supratentorial reperfusion patterns. The altered cortico cerebellar circuits responsible for CCD can be visualized by diffusion tensor MRI.\textsuperscript{25}

Stroke recovery has been investigated using MRI methods, with changes in both structure and function identified in human gray matter\textsuperscript{26,27} and in white matter anodetically and more carefully in animal studies,\textsuperscript{28} with new MRI methods for quantifying changes in white matter such as diffusion tensor and diffusion spectrum imaging\textsuperscript{29} showing particular promise. Given the tremendous morbidity from stroke and the challenges to delivery of acute treatment, these areas are particularly important and developments in these areas particularly welcome. New methods for tracking cellular therapies in humans\textsuperscript{30} hold out promise that imaging may assist chronic recovery strategies.

Finally, imaging is playing a key role in the unraveling of one of the most significant challenges of stroke, that of understanding its genetics. White matter hyperintensities have been known to have a heritable component for some time (with heritability in one twin study was reported at 0.73\textsuperscript{31}). Although our understanding of white matter hyperintensities is incomplete, there does seem to be evidence that white matter hyperintensities, as seen on MRI, are associated with hypertension, stroke, and possibly worse outcome of the penumbra; in 2006 a genome-wide scan demonstrated evidence that a gene on chromosome 4 may influence these white matter hyperintensities.\textsuperscript{32} The increasing power of imaging to understand and quantify changes in white matter may allow greater insight into the link between stroke and genetics.

Similarly exciting advances have been made in hemorrhagic stroke over the past year, with all diagnostic modalities coming to bear on this illness as well, but space will not allow a full review. Suffice it to say that imaging in stroke remains a fast-moving and innovative area of stroke research.

Disclosures

Neither author has any conflicts of interest to disclose relevant to this article. Dr Sorensen’s relationships are posted at www.biomarkers.org.

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