Role of imaging in treatment trials

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Treatment trials in vascular causes of dementia have progressed slowly due to multiple factors including, heterogeneous patient populations and lack of suitable end points. However, selection of homogeneous subpopulations of vascular cognitive impairment (VCI) patients is now possible with the use of multimodal biomarkers that identify patients with white matter lesions that are more likely to have a progressive course. In addition, treatments are emerging from animal models of white matter disease. With improved classification methods, smaller homogeneous study populations, and potential drugs, it is important to determine the optimal end points to use in human treatment trials. Imaging methods provide several options to determine the success of a novel treatment. Initial emphasis was placed on the growth over time of white matter hyperintensities (WMHs), which can be quantified and measured noninvasively over extended periods of time in large populations. However, WMHs are also found in normal elderly unrelated to symptoms, making them unreliable biomarkers in smaller, non-population-based studies. Alternatively, proton magnetic resonance spectroscopy (1H-MRS) and diffusion tensor imaging (DTI) provide a more accurate indication of ischemic injury than WMHs. Inflammatory biomarkers provide another end point. Dynamic contrast-enhanced MRI (DCEMRI) shows regions of inflammation and provides quantitative data on the extent of blood-brain barrier (BBB) disruption. While BBB permeability provides a short-term end point that fluctuates, DTI and 1H-MRS show changes over longer terms that are not reversible, and are easily quantifiable. Cognitive measures are also useful, but the time course for their changes is generally years. The current challenge is to identify the optimal imaging biomarkers, alone or in combination, can provide appropriate information on which to base the success or failure of a new treatment in VCI.