Subtle BBB-Breakdown Detection in Neurodegenerative Disease

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There is growing interest in investigating the role of subtle changes in blood-brain barrier (BBB) function in common neurological disorders, such as dementia [1,2], Alzheimer’s disease [3], type II diabetes [4] and cerebrovascular disease [5,6]. Several studies have used dynamic contrast-enhanced MR imaging (DCE-MRI) to assess the state of the BBB in these diseases and have demonstrated much smaller post-contrast signal changes in the tissues of interest than obtained from more traditional approaches. For example, in intracranial tumours and multiple sclerosis. Conflicting results have been reported, but there is increasing evidence, both from DCE-MRI studies, and elsewhere, that the BBB plays an important role in these disease processes.

Using typical DCE-MRI sequences, maximum post-contrast signal changes in subtle disorders are around 5% in grey matter and 1 – 2% in white matter with changes over the imaging period being on the order of 1 – 2%. This is in contrast to measurements in tumors, where signal enhancement on the order of 100%, or 50%, respectively, is commonly encountered. As a result, the small changes associated sub-BBB effects are significantly influenced by scanner noise and typically require large sample sizes to minimise random noise and identify any differences between study and control populations [7]. In general, contrast agent accumulation has been measured for a longer period of time than in conventional DCE-MRI studies, with imaging typically being performed for anywhere from 30 minutes to several hours. It is unclear, at present, whether this is necessary to characterise the leakage properties, although it does have the advantage that more data points can be acquired, which is beneficial for reducing the influence of scanner noise. As it is expected that exchange between the vasculature and extravascular extracellular space will be slow, individual measurements are typically acquired at a lower temporal resolution than for those applications where rapid exchange is expected. This, again, has the benefit of increasing signal-to-noise of the acquired images.

To-date, the majority of studies have investigated differences in signal enhancement properties only, inferring a direct relationship to BBB breakdown, and have not attempted to perform quantification of contrast agent concentration or pharmacokinetic parameters. This is primarily due to individual data points being too noisy to reliably facilitate model fitting. However, voxel-by-voxel estimation of permeability has recently been performed in patients with vascular cognitive impairment (VCI) with encouraging results [8]. This method utilised a reduced contrast agent dose, in combination with direct T1 measurement, and permeability estimated using Kalman filtered Patlak plots. It remains to be seen whether this method can be applied more widely to the full spectrum of subtle BBB disorders, where post-contrast signal change may be lower than in VCI. There is certainly considerable future scope for development and evaluation of models suitable for quantification of subtle BBB disorders.

Reliable quantification of permeability remains the ultimate aim because inferring that signal enhancement directly relates to the amount of extravascular contrast agent present and hence degree of BBB permeability is frequently a flawed assumption [7]. Many parameters have an effect on the relationship between measured signal enhancement in DCE-MRI and extravascular contrast agent concentration, such as the intrinsic pre-contrast T1 of the tissue (T10), the contrast agent relaxivities (r1 and r2), as well as the influence of intravascular contrast. Many of these parameters are expected to be altered by disease processes, yet are frequently assumed to take normal values, or not accounted for at all, leading to errors when estimating the contrast agent concentration. In general, simple compartmental models are assumed to describe the relationship between the contrast agent distribution between vascular and extravascular extracellular spaces, but these may not be appropriate for slow leakage where recirculation of contrast agent via the CSF may play a significant role [4]. It is unclear whether more appropriate (and complex) models could be supported by the data, as model fitting to a limited number of noisy DCE-MRI data points is a challenging prospect. When applying such models to quantify permeability, it is essential that the sources of error are well understood and that the models are not just applied as a ‘black box’. Without these limitations being properly understood, it is likely that the resulting quantitative estimates of permeability are no more informative than simple measures of signal enhancement, particularly if a suitable control population is selected.

In conclusion, DCE-MRI of subtle BBB breakdown is a relatively new and challenging research topic, with significant work still required before reliable quantification can be obtained. There are many avenues of future research that would improve the method, including developing more sensitive hardware, novel contrast agents that result in a greater signal change or offer more specificity with regard to the BBB target, while there is still a

great deal of work to be done to understand the limitations of the current techniques. Nevertheless, DCE-MRI appears to be playing a key role in developing our understanding of BBB breakdown in neurodegenerative diseases.

References: