Enlarged Perivascular Spaces: How Prevalence Might Influence Gene Therapy Trial Design

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TARGET AUDIENCE: This information will benefit scientists and clinicians working in the field of convection enhanced delivery (CED) of therapeutic drugs to the brain. It will be of particular interest to those who are focusing on gene therapy within structures of the basal ganglia, especially those targeting the putamen for Parkinson's disease (PD).

PURPOSE: Perivascular spaces (PVS) are cavities surrounding blood vessels and are believed to contain cerebrospinal fluid (CSF). Under the pressure of a CED procedure, perivascular spaces act as unwanted escape routes for the infusate being injected. Work done by our group illustrates how PVS cause unwanted variability of CED infusate distributions in animal models, as seen in Figure 1.

Atypical enlarged PVS (EPVS) are present in an unknown percentage of human putamen, the gray matter structure commonly considered in gene therapy trials for Parkinson's disease, and may cause variability in the infusate distribution. This work aims to estimate their prevalence in the putamen in a cohort with age similar to PD patients. Knowledge of the prevalence would influence the effort expended to detect and track their unwanted effects in dosage distribution in possible upcoming clinical trials.

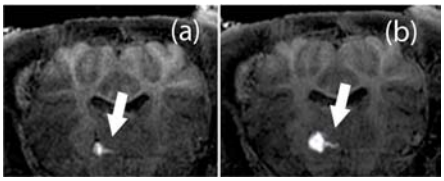

Figure 1. Time series of in-vivo CED experiment shows infusate doped with Gd-DTPA following unwanted medial leakage pathway (arrows) towards the midline near the start of infusion (a), and the end, 7 min later (b).

METHODS: Previous efforts have not determined prevalence within specific brain structures of the basal ganglia. We utilized an existing database of cognitively normal, healthy adults enrolled in a longitudinal study on Alzheimer's disease. We examined data from the 155 subjects who had T1, FLAIR, and T2 scans all performed in the same visit. Their mean age, 59.8 ± 5.97 years, is similar to the mean age of onset in Parkinson's disease. EPVS < 2mm are deemed small in a seminal review paper on EPVS[1]. We classified subjects as atypical if they had two or more medium (2-5 mm diameter), or one or more large (>5 mm) EPVS in the putamen.

The sequences examined in this study were 3D acquisitions with whole brain coverage and 256x256 voxels in plane – axial FSPGR T1-w (1mm isotropic voxels), sagittal FLAIR (1x1x2mm voxels), and sagittal T2-w (1mm isotropic). Datasets were viewed in the axial plane (with reformatting for T2 and FLAIR) and features suspected to be enlarged PVS were identified and confirmed by simultaneous viewing of T1 and T2 data for a given slice. In one instance, FLAIR images were used to rule out a feature that was not an EPVS but likely an old lacunar infarction[1].

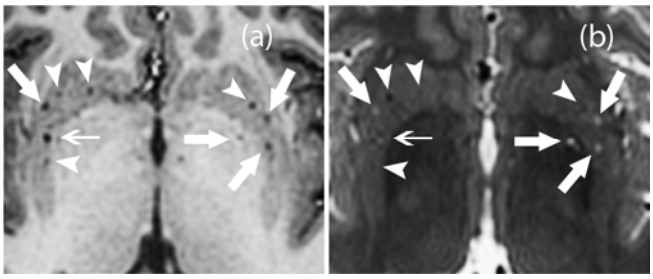

Figure 2. T1-W (a) and T2-W (b) images of an example human brain showing EPVS, hypointense in T1 and hyperintense in T2 (arrows), and normal vessels, hypointense in both (arrowheads). The thin arrow indicates a structure in the right putamen that is possibly a confluence of multiple vessels. (Image contrast set very high for conspicuity).

RESULTS: Differentiation of EPVS from blood vessels is illustrated in Fig. 2, with EPVS appearing hyperintense in T2-W images (Fig. 2b) and both structures appearing hypointense in T1-W imaging (Fig. 2a). Fifteen of 155 subjects were classified as having atypical EPVS in the putamen. Four had atypical vasculature near, but just outside the putamen, and 136 were deemed normal.

DISCUSSION: Atypical vasculature was identified in 19 out of 155 (12%) subjects either within or adjacent to the putamen. Considering all subjects participating in a CED-based gene therapy drug trial would receive preoperative brain MRI, those Phase I subjects who have atypical EPVS would merit MR-based quantification of infusate distribution during the procedure. Depending on the degree of infusate loss, the presence of EPVS may be useful as an exclusion criterion during latter phases of the clinical trials. A semi-quantitative rating scheme[2] assigns a grade based solely on a count of EPVS. Since the size of EPVS may be relevant to their role as channels for infusate loss, existing rating schemes may be inadequate for predicting likelihood of unwanted infusate loss.

CONCLUSIONS: We have shown the prevalence of atypical perivascular spaces in the putamen in a moderate-sized cohort of healthy subjects with average age similar to the average age of Parkinson's disease onset. Detecting EPVS in subjects prior to treatment and then monitoring infusion distribution in those subjects seems worthwhile, given a prevalence of 12% and the modest effort needed.

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