Review of: "Semi-automated Segmentation and Quantification of Perivascular Spaces at 7 Tesla in COVID-19"

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Langan et al. (Langan et al. 2022) conducted a case-control study in COVID-19 patients complaining about neurological symptoms (n=10) compared to age- and sex-matched controls without a history of COVID-19 (n=9). The authors applied axial T2-weighted magnetic resonance imaging (MRI) acquired with the high-resolution capabilities of ultra-highfield (UHF) MRI (0.2 × 0.2 × 2 mm resolution at 7T) and presented a semiautomatic segmentation tool for tracing perivascular spaces (PVS) in 2D with high accuracy. This cutting-edge approach allowed for the quantification of several PVS features, such as density, count, volume, diameter, and length. Whole-brain PVS count and white matter hyperintensity (WMH) volume were significantly higher in the patient group, however, effect size was not reported nor were the results adjusted for multiple testing. Besides some large effect size associations between body mass index (BMI), PVS count and WMH volume, MRI measures did not relate to any clinical variable comprising further cardiovascular risk factors, self-reported symptoms or duration of hospitalization.

Unfortunately, it is unclear whether COVID-19 infection has been proven (patients) or excluded (controls) through laboratory testing or self-tests. One additional major caveat was the only subjective report of various psychiatric or neurological symptoms by the patient group without any external validation or quantification. Further, the available information of COVID-19 severity and duration of hospitalization have not been investigated. Although the presented cohort is relatively small, rendering generalization of potential findings non-trivial, there is untapped exploratory potential. The absence of detailed information about the control cases, especially with regard to concomitant systemic diseases and vascular risk factors, is another limitation. Further, the large variance of the timespan between recovery and the 7T scan (between 50 to 596 days, median of 580 days) for the patient group and its effect on the study has not be reported. Together with rather small sample sizes, the above-mentioned sources of (potential) intra-group heterogeneities might have hindered finding additional group differences or clinical associations.

Although the level of detail provided by UHF MRI is impressive, even at clinically available field-strength, enlarged PVS (EPVS) become visible as small, fluid-filled structures that parallel the direction of perforating vessels, especially in the white matter of the centrum semiovale (CSO), basal ganglia, hippocampus and midbrain. EPVS and its greater frequency, i.e. severity, especially surround arterioles, have been discussed indicative of perivascular fluid accumulation that point towards perivascular waste/fluid clearance failure certainly in aging, cerebral small vessel disease (CSVD) or

neurodegeneration. EPVS have in that recently considered one of several MRI markers for CSVD diagnosis (Wardlaw et al. 2013; Charidimou et al. 2022). PVS enlargement is accompanied by small vessel wall alterations and perivascular inflammatory cell infiltration, which goes along with blood-brain barrier (BBB) breakdown (for review please see Wardlaw et al. 2020).

COVID-19 patients interestingly reveal an endothelial dysfunction with endothelial/microvascular inflammation, accompanied by angiogenetic alterations, microthromboses, ischemic lesions affecting several organs also comprising the brain and thereby in part mimicking CSVD-related changes (Bonaventura et al. 2021; Hanafi et al. 2020). Elevated plasma pro-inflammatory cytokines, which are commonly also found in CSVD, may further increase vascular permeability exaggerating BBB impairment during COVID-19 infection (Che Mohd Nassir et al. 2021). Arguably, COVID-19 infection might impact the onset or progression of CSVD probably also interfering with perivascular clearance function.

The strengths of the study conducted by Langan et al. is the combination of UHF MRI and semiautomatic segmentation in COVID-19 to reliably detect PVS in 2D. As mentioned by the authors, this 2D-based image acquisition with thick slices and a slice gap as inherent challenges. Since the 2D images are also processed individually, PVS propagating through multiple slices might cause overestimation of PVS counts. Potentially, this is exacerbated further due false positives caused by image features with similar contrast as PVS in T2-weighted images such as small lacunes or from motion artefacts (Potter et al. 2015). Beyond the PVS count, 2D PVS assessment renders the computed morphological features, such as volume, diameter and length, less reliable since the PVS might extend through the individual slice. Although the imaging resolution used here is exceptional compared to other studies, 3D imaging approaches with isotropic resolution would enable true 3D PVS quantification. The authors claim that 3D TSE would result in less uniform contrasts, but this challenge can be corrected effectively for with prospective (parallel transmission or dialectic pads) and retrospective (bias field correction) approaches. Further, using thick slices might be a bias in PVS detection and assessment. For axial slices, the majority of PVS in the CSO run parallel to the 2D slice while in the basal ganglia the majority of PVS is oriented orthogonal to the imaging slice. This potential regional differences were not taken into account by the authors. Further, metrics for regional PVS, such as in CSO, basal ganglia, hippocampus or midbrain, which are the hallmark areas, could have been reported. This might at least in part explain the absent link between vascular risk factors and whole-brain PVS metrics, as certainly PVS in deep brain regions, e.g. basal ganglia, but not in the CSO, have shown associations.

The authors conclude that higher PVS frequency and larger WMH volumes in COVID-19 might indicate neuroinflammatory processes. Indeed, results could also point towards (additional) alterations of perivascular clearance (see above). Further, COVID-19 patients could just have suffered from more advanced, already pre-existing, CSVD predisposing these patients to neurological or psychiatric symptoms during and after infectious disease, commonly observed as a more non-specific CNS reaction against fever or any infectious disease state.

In the future, longitudinal data acquisition could help to better distinguish between PVS- or WMH-related neuroinflammation, in terms of BBB breakdown, or perivascular clearance failure and the chicken-egg-problem of what is

first, CSVD predisposing to COVID-19 infection or COVID-19 predisposing to CSVD onset or its more rapid progression. Future studies should further combine *in-vivo* imaging and biofluid approaches taking account of e.g. measuring circulating microparticles indicative of endothelial activation/dysfunction and neurovascular unit alterations, such as glial or pericytic markers, to gain a deeper understanding of the underlying processes of PVS frequency increase in human health and disease, especially COVID-19 (Che Mohd Nassir et al. 2021).

Overall, this cutting-edge study provided a glimpse into the potential interplay of COVID-19, PVS, neuroinflammation, and the glymphatic system, but further methodological advancements, larger cohort, additional bloodwork, and longitudinally data acquisition are required to generalize the results presented by Langan et al.

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