Pathophysiologically relevant perivascular processes in multiple sclerosis – can we detect them in vivo by MRI?

J. T. Wuerfel[1], M. Haertle[1], F. Paul[1], H. Waiczies[1], and F. Zipp[1]
[1]Molecular Neurology, Charite University Medicine Berlin, Berlin, Berlin, Germany

Introduction

The perivascular compartment surrounding small cerebral arteries and arterioles (Virchow-Robin spaces, VRS), has been in the focus of neuroimmunological research for decades, although its role for lymphocyte trafficking into the brain was not appreciated until recently [1, 2]. Despite generally growing interest in the function of VRS in inflammatory, vascular and other cerebral pathologies [3-6], only few *in vivo* studies in multiple sclerosis (MS) have addressed this aspect so far [7-9]. Thus, it is still under heated debate, whether VRS, as depicted by MRI, represent neuroimmunological activity, a hypothesis that was supported by a recent post mortem study revealing enlarged VRS in MS patients [10]. In a quantitative, semiautomated multi-modal MRI approach, we here investigated the number and volume of VRS in the basal ganglia of MS patients in comparison to matched healthy controls.

Methods

45 MS untreated patients (23 female, age range 22-57ys.) with relapsing-remitting disease course (RRMS) and 24 matched healthy controls (16 female, age range 24-57ys.) were investigated on a Siemens Sonata 1.5T scanner (Siemens Medical Systems, Erlangen, Germany) using a quadrature head-coil and standard Siemens sequences (T1-weighted 3D [MPRAGE: 1x1x1mm^3, TE 4.38ms, TR 2110ms, TI 1100ms, flip angle 15°], axial T2-weighted [TSE: 44 slices, thickness 3mm, no gap, TE 13ms, 81ms and 121ms, TR 578ms, flip angle 150°, FOV 256x256] and axial fluid attenuated inversion recovery [TIRM: 44 slices, thickness 3mm, no gap, TE 108ms, TR 10000ms, TI 2500ms, flip angle 150°, FOV 256x256]) (Figure 1). VRS were anatomically identified on 3D MPRAGE; small MS lesions could be excluded on corresponding TIRM slices. For quantitative analysis, VRS were assessed on corregistered T2-weighted (TE 121ms) scans, applying the semiautomated MEDx3.4.3-software (Medical Numerics, Sterling, Virginia, USA), as described previously [11]. Ten patients were investigated at different time points with and without disease activity, defined by Gd-DTPA enhancing lesions (CELpos. or CELneg.).

Results and Discussion

On high resolution MRI, we identified VRS of the basal ganglia in each investigated subject. Our quantitative analysis revealed significantly higher VRS volumes in MS patients compared to healthy controls (p=0.012, Mann-Whitney U). In contrast, VRS count did not differ significantly between these two groups (Table 1). Although VRS volumes and counts increased with age (data not shown), this was not a cofounding effect between the two groups. VRSs data will further be correlated to brain parenchymal fraction measurements to rule out atrophy as unique factor for VRSs increase. The effect of disease activity on VRS was investigated in 10 patients where we acquired longitudinal data. At time points of Gd-DTPA enhancement, the VRS volumes of these patients increased significantly (p=0.022, Wilcoxon signed ranks), although VRS counts remained constant (Table 2). VRS volume might therefore serve as a parameter for disease activity in MS.

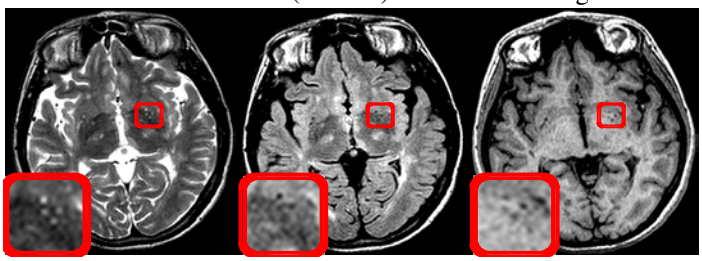

Figure 1: *Coregistered T2w, TIRM and MPRAGE images. VRS in basal ganglia highlighted.*

Group	Number	Age (SD)	Count (SD)	Volume (SD)
RRMS patients	45	39.7 (8.2)	21.9 (9.2)	198.3* (90.4)
Healthy controls	24	36.8 (11.3)	19.3 (5.8)	143.6* (57.8)

Table 1: *Mean VRS counts and volumes. *significant group difference. SD = standard deviation.*

Conclusion

VRS of the basal ganglia area can be quantified by high resolution MRI. Perivascular accumulation of macrophages and lymphocytes, a prominent feature of MS pathology, is likely reflected in increased VRS volumes

References

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Group	Count (SD)	Volume (SD)
CEL pos.	16 (5)	180.7*(49.6)
CEL neg.	13.7 (5)	154*(61.5)

Table 2: *Mean VRS counts and volumes of 10 patients. Visit with contrast enhancing lesions (CEL pos.) or without (CEL neg.) *significant group difference.*
SD = standard deviation.