Dilated Perivascular Spaces: Hallmarks of Mild Traumatic Brain Injury

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BACKGROUND AND PURPOSE: Recent animal and human studies have shown an increased frequency of enlarged, high-convexity Virchow-Robin spaces (VRS) in several neurologic diseases, suggesting their role as neuroradiologic markers of inflammatory changes. The aim of this study was to determine the prevalence of high-convexity dilated VRS in mild traumatic brain injury (TBI).

METHODS: T2-weighted, T1-weighted, fluid-attenuated inversion recovery, and T2*-weighted gradient-echo brain MR images were acquired in 24 patients with TBI (10 women, 14 men; mean age, 33.6; range, 18.1–50.8 years) and 17 age- and sex-matched healthy control subjects (nine women, eight men; mean age, 32.8; range, 18.4–47.8 years). The mean interval after TBI was 3.6 days (range, 1–9 days) in 15 patients and 3.7 years (range, 0.6–13.4 years) in nine patients. Axial T2-weighted images were used to identify dilated VRS and to measure CSF volume; T1-weighted images were used to measure brain volume. Dilated VRS were identified as punctuate areas with CSF-like signal intensity in the high-convexity white matter.

RESULTS: Mean (± standard deviation) number of VRS was significantly higher in patients (7.1 ± 4.6) than in controls (2.4 ± 2.9, P < .0003). In controls, VRS were associated with age (R = 0.69, P < .001) whereas in patients, they neither correlated with brain and CSF volumes nor with age and the elapsed time from injury.

CONCLUSION: Our results suggest that the increased number of dilated VRS is a radiologic marker of mild head injury that is readily detectable on T2-weighted images. Because their number does not vary with time from injury, VRS probably reflect early and permanent brain changes.

Perivascular spaces, or Virchow-Robin spaces (VRS) are extensions of the subpial space surrounding perforating arteries and emerging veins from the cerebral cortex (1). Lenticulostriate VRS follow the path of the homonymous arteries as they enter the basal ganglia through the anterior perforate substance. They are commonly seen around the anterior commissure in normal subjects (2). High-convexity VRS follow the path of penetrating cortical arterioles and are usually detected at the level of white matter. On conventional MR imaging scans they are detectable in only 13% of healthy adults and in only 3% of children between 20 months and 16 years of age (3, 4). While small (< 2 mm in diameter) VRS represent an anatomic variant (3), large VRS have been associated with age, dementia, and incidental white matter lesions (3). An increased number of high-convexity white matter VRS has been described in patients with multiple sclerosis and attributed to early inflammation (5). In addition, brain trauma studies in rodents have demonstrated an inflammatory infiltrate temporally and anatomically associated with early breakdown of the blood-brain barrier (BBB) breakdown (6, 7). More recently, a strong perivascular and parenchymal posttraumatic inflammatory reaction was confirmed in contused human brain tissue (8).

The reported inflammation in severe traumatic brain injury (TBI) and the association between enlarged VRS and inflammatory infiltrate in experimental trauma models and in neurologic disorders led us to hypothesize that mild TBI is associated with changes in VRS. Therefore, we evaluated the prevalence of high-convexity dilated VRS in patients with mild TBI compared with age- and sex-matched healthy control subjects. To investigate whether dilated high-convexity VRS spaces are a transient, post-
traumatic phenomenon, the patients with TBI were stratified into two groups: one imaged within 7 days of trauma and the other imaged within a mean of 4 years after injury.

Methods

Subjects
We examined 24 consecutive patients with TBI (10 women, 14 men; mean age, 33.6 years; range, 18.1–50.8 years) who met the following inclusion criteria: 1) mild, closed head injury; 2) no evidence of systemic, psychiatric, and other neurologic illnesses; 3) no evidence of imaging findings unrelated to trauma; and 3) age of 18 years or older. All patients were screened by means of their medical history and physical examination findings to exclude alcohol abuse, cardiovascular risk factors, hypertension, and diabetes mellitus. Mild head trauma was classified according to the definition developed by the Mild Traumatic Brain Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine, as reviewed by Esselman and Uomoto (9). The definition includes loss of consciousness of less than 20 minutes, post-traumatic amnesia of less than 24 hours, and an initial Glasgow Coma Scale (GCS) score of 13–15. Fifteen patients underwent MR imaging within a mean interval of 3.6 days (range, 1–9 days) after the traumatic incident, and nine patients, after an average of 3.7 years (range, 0.6–13.4 years). Seventeen age- and sex-matched healthy volunteers (nine women, eight men; mean age: 32.8 years; range: 18.4–47.8 years) underwent the same MR imaging procedures. Our institutional review board approved the study, and all subjects provided written informed consent.

Image Acquisition
MR imaging was obtained by using a 1.5-T MR unit (Vision; Siemens, Erlangen, Germany). The protocol included axial dual spin-echo sequence (TR/TE1/TE2/TR = 7900/17/19; 25 contiguous sections, 3-mm thickness; FOV, 220 × 220 mm; data matrix, 190 × 256; flip angle, 180°), sagittal T1-weighted Magnetization Prepared Rapid Gradient sequence (TR = 9.7/4; section thickness, 1.5-mm; FOV, 210 × 210 mm; matrix 256 × 256; flip angle, 15°), axial fluid-attenuated inversion recovery (FLAIR) sequence (TR/TE/T1 = 9000/92/2500; 25 contiguous axial sections, 5-mm thickness; FOV, 240 × 240; matrix 256 × 256; flip angle, 180°), and T2*-weighted gradient-echo sequence (TR/TE = 1020/22; section thickness, 5.0 mm; gap, 1.5 mm; FOV, 220 × 165 mm; matrix 192 × 256; flip angle, 30°). Two neuroradiologists (M.I., R.I.G.) who were unaware of the clinical diagnosis independently assessed the images for any remarkable structural abnormalities, including microinfarcts and gliotic spots in the region of the small penetrating arteries and arterioles.

Identification and Quantification of VRS
Enlarged VRS were visually identified on all axial 3-mm-thick T2-weighted sections between the superior margin of the corpus callosum and the upper level of the brain according to the following criteria: 1) punctuate white matter areas brighter than the surrounding tissue and 2) punctuate areas smaller than 2 mm in diameter (one to three pixels) conforming to the path of penetrating arteries (3, 5). Figure 1 shows examples from patients and control subjects. Two neuroradiologists (M.I., R.I.G.) independently assessed the number of dilated VRS, and their number was recorded on the section showing the maximum number. Disagreements were resolved by a consensus reading. A separate blinded study of interobserver variability established an excellent reader agreement on the number of dilated VRS, with \( \kappa = 0.996 \) (95% confidence interval: 0.985, 0.998).

Volumetric Image Analysis
T1-weighted and T2-weighted images were analyzed by using a software package developed in-house, the Multimodal Image Data Analysis System package, (10) on a workstation (Sun Microsystems, Palo Alto, CA). In each subject, brain parenchyma and CSF volumes were measured. Sagittal T1-weighted images were processed as follows: A 30-ml seed region was placed bilaterally in the periventricular white matter to normalize the MR signal intensity among subjects. An over-inclusive mask was then extracted by selecting the set \( W \) of all voxels at intensity >0.55 \( S_W \), where \( S_W \) is the average signal intensity of periventricular white matter (11). A region growing algorithm was then applied to restrict \( W \) to the brain tissue alone (10). The final brain mask was truncated at the level of the foramen magnum to incorporate the brain stem and cerebellum but not the spinal cord.

Axial T2-weighted images were used to measure CSF volume. A 0.5–1.0-mL sample of pure CSF was selected in the area of lateral ventricles free of visible choroids plexus and its intensity \( S_C \) measured to achieve signal intensity normalization. CSF voxels were defined as those with signal intensity >\( K_S \), where \( K \) is the phantom-derived constant parameter that provided an unbiased separation between CSF and brain parenchyma on our T2-weighted images. Finally, brain parenchyma and CSF volumes were calculated by multiplying the number of voxels within the respective masks by the voxel volume (1.009 mm\(^3\) for T1-weighted images and 2.017 mm\(^3\) for T2-weighted images).

Statistical Analyses
A two-tailed Student t test for nonpaired data were used to compare the number of VRS between all patients and all control subjects and between the two subgroups of patients. A linear regression model was used to assess the correlation between the number of dilated VRS and the brain and CSF volumes. A \( P \) value of <.05 was considered to indicate a statistically significant difference.

Results
Table shows the demographic data for the 24 patients, including age, sex, elapsed time from TBI, GCS score, cause of injury, and MR imaging findings related to trauma. All patients but one had a GCS score of 15. Motor vehicle accidents or falls accounted for 80% of the injuries. Trauma-related MR imaging findings were unremarkable for nearly all patients: Three had a contusion, and one had a subdural hematoma. Neither foci of microhemorrhage nor lesions suggestive of diffuse axonal injury were seen on any of the T2*-weighted gradient-echo images from patients.

No abnormalities were identified on MR images in the healthy volunteers. The mean number of dilated high-convexity VRS visualized on consecutive T2-weighted images was higher in patients (7.1 ± 4.6) than in control subjects (2.4 ± 2.9, \( P < .0003 \)), whereas it was similar in patients with a short delay and those with a long delay after trauma (6.9 ± 4.9 and 7.5 ± 4.2, respectively). High-convexity VRS appeared isointense relative to the surrounding brain on FLAIR images. We observed no significant difference between patients and control subjects in terms of mean brain volume (1287 ± 116 and 1332 ± 128 mL, respectively) and mean CSF fraction, i.e., the fraction of cranial volume filled with CSF (9.6% ± 3.5% and
The number of VRS was associated with age in control subjects \((R = 0.69, P < .001)\) but not in patients with TBI (Fig 2). Among patients, dilated VRS were not correlated with brain and CSF volumes or with the time after injury.

### Discussion

Although CT scanners allow the visualization of pathologic processes dilating the VRS, it is only with the advent of high field MR imaging imagers that the fluid-filled space surrounding arteries, arterioles, veins, and venules are routinely visualized (12). The basement membrane of the glia limitans peripherally lines the fluid-filled perivascular space (1), and macrophages and cells of fibroblastic origin surround the vessel in its center (13). On MR images, VRS are routinely detected as small (<2 mm in diameter), circular foci of CSF-like signal intensity. In the present study, we observed an increased prevalence of dilated VRS in the high-convexity white matter in patients with mild TBI compared with sex- and age-matched healthy control subjects. Approximately 80% of the annual 2,000,000 new cases of TBI in the United States are classified as mild, with a peak of incidence in individuals aged 15–24 years (14).
Demographic data and trauma-related imaging findings in 24 patients with TBI

<table>
<thead>
<tr>
<th>Patient/ Age (y)/ Sex</th>
<th>Delay after TBI (d)</th>
<th>GCS Score</th>
<th>Cause of TBI</th>
<th>Trauma-Related MR Imaging Findings</th>
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<tbody>
<tr>
<td>1/35/F</td>
<td>1</td>
<td>15</td>
<td>MVA</td>
<td>Unremarkable</td>
</tr>
<tr>
<td>2/46/F</td>
<td>1</td>
<td>15</td>
<td>MVA</td>
<td>Unremarkable</td>
</tr>
<tr>
<td>3/31/F</td>
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<td>15</td>
<td>Fall</td>
<td>Unremarkable</td>
</tr>
<tr>
<td>4/29/M</td>
<td>1</td>
<td>15</td>
<td>Fall</td>
<td>Subdural hematoma</td>
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<tr>
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<td>15</td>
<td>MVA</td>
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<td>15</td>
<td>MVA</td>
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</tr>
<tr>
<td>7/30/M</td>
<td>2</td>
<td>15</td>
<td>BI</td>
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</tr>
<tr>
<td>8/42/M</td>
<td>2</td>
<td>15</td>
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</tr>
<tr>
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<td>Fall</td>
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<td>7</td>
<td>15</td>
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<td>15</td>
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<td>15</td>
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<tr>
<td>15/36/F</td>
<td>9</td>
<td>15</td>
<td>Fall</td>
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<tr>
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<td>MVA</td>
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</table>

Note.—BI = blunt injury, MVA = motor vehicle accident.

Although conventional MR imaging shows no abnormality in most cases, 30% of patients with mild TBI have some degree of neurologic or cognitive deficit (15). Increasing evidence shows that even mild TBI can cause brain damage, suggesting that structural and physiologic factors may contribute to some cognitive symptoms and postconcussive syndrome (16). Results of pathologic studies suggest that diffuse axonal injury may account for these persistent problems (17).

To our knowledge, this is the first time that the presence of enlarged VRS has been described in human TBI. In our cohort, the number of VRS was not correlated with age, time from injury, or brain or CSF volumes.

Although dilated high-convexity VRS have been described in healthy subjects and in association with several neurologic diseases (4, 18–21), the mechanism underlying the enlargement of the perivascular space is not well established. Heier et al reported that age, hypertension, dementia, and incidental white matter lesions are significantly associated with large VRS (3). After multivariable logistic regression analysis, however, only age remained significant, suggesting that the widening of VRS is an aging phenomenon. Hughes (22) attributed the enlargement of VRS to the spiral elongation of arteries to elevated blood pressure, and Awad et al (23) suggested that dilated VRS reflect ex vacuo brain atrophy. Neither the unfolding of tortuous vessels nor brain atrophy is likely to account for the widening of VRS in our patients, as we did not find any correlation with age or with CSF or brain volume.

In some neurologic diseases, such as encephalitis, meningitis, and neurosarcoidosis, inflammatory cells fill the VRS and likely play a major role in cell-mediated immune reactions (1, 18). In addition, Achiron and Faibel (5) suggested that VRS may represent neuroradiologic markers of inflammation in patients with recent-onset multiple sclerosis. Specifically, VRS may provide the setting in which macrophages process foreign antigens and convey them to local lymph nodes, where they are accessible to a larger number of cells. Once activated, these cells may accumulate in the VRS, possibly generating a full-blown immune response.

Interestingly, experimental studies of brain trauma have demonstrated an inflammatory infiltrate temporally and anatomically associated with early BBB injury (6, 7). In rodents, few minutes after the injury, the influx of the second messenger Ca$^{2+}$ activates phospholipase A$_2$ and cyclo-oxygenases (COX) which, in turn, induce lipid peroxidation, subsequent damage to the cell membrane, and the release of toxic prostanooids and reactive oxygen species (24). Another proinflammatory cytokine expressed by microglia/macrophages, the endothelial monocyte-activating polypeptide II (EMPA II) accumulates in rodent brains after traumatic injury (25). Most notably, this posttraumatic inflammation is associated with the clustering of both COX-1$^+$ and EMPA II$^+$ microglia and macrophages in the VRS of the injured brain (24). These cells reach maximum density at days 5 and 7 after injury, paralleling the infiltration of blood-borne cells, such as lymphocytes and monocytes, and then decline until 21 days after injury. Experimental studies have also indicated that inflammatory mechanisms are involved in the pathogenesis of early and
delayed axonal injury after contusion (26). Importantly, Holmin et al (8) demonstrated that these findings in rodents are applicable to humans with brain contusion. An inflammatory reaction is detected in contused brain tissue in patients who undergo surgery 3–5 days after trauma. In the early phase (<24 hours) the inflammation is perivascular and dominated by polymorphonuclear cells, whereas in the delayed phase (3–5 days), inflammation is more evident in the parenchyma (8). By analogy with the experimental studies, the authors suggest that the inflammatory reaction might cause cellular degeneration and BBB damage, providing a substrate for long-term degenerative effects.

All of these observations support the role of inflammation in moderate-to-severe TBI. Our findings suggest that an inflammatory component affects brain parenchyma, albeit at a low level, during mild TBI. We believe that the enlargement of the perivascular space might reflect the accumulation of inflammatory cells and/or changes of vascular permeability (27). Dilated VRS could provide a passive access to CNS of blood-borne cells, which, in turn, could trigger or enhance the inflammatory process. Inflammatory cells produce free radicals and cytokine, which are destructive to surrounding cells, such as neurons and oligodendrocytes. Prolonged presence of these cells or their sustained inflammatory cytokine-producing state could lead to posttraumatic axonal degeneration. If confirmed, these findings might have important pathologic and clinical implications, allowing the early detection of morphologic and physiologic abnormalities leading to axonal injury and, perhaps, preventing it with targeted treatments.

Other mechanisms could have contributed to the enlargement of the perivascular space in TBI patients. It is well established that rotationally induced shear-strain injury produces lesions at one of four topographic levels: cortical surface, cerebral white matter, brainstem, and penetrating blood vessels (arteries and veins). Typically, neurons are the most susceptible to shear-strain deformations because of their inherently low rigidity. However, nonneuronal tissue, such as penetrating blood vessels, bridging veins, and pia-arachnoid may also be injured (28). Accordingly, the number of dilated VRS is expected to be higher in association with typical shear-strain injuries, such as contusion and subdural hematoma, than with others. Although we cannot rule out the contribution of induced shear-strain stretching on the perivascular space enlargement, the number of dilated VRS did not differ between patients with trauma-related MR imaging findings and patients with normal brain MR images.

Unlike Heier et al (3), who detected high-convexity VRS in 13% of healthy control subjects, we detected them in 76% of our control subjects. We believe that this difference was related to higher contrast between CSF and brain tissue due to the longer TE of our spin-echo sequence and to the use of contiguous 3-mm-thick sections instead of the 5-mm thick sections with 2.5–5-mm gap Heier et al used. This reason is in line with the results of Rollins et al (4), who showed that three-dimensional, gradient-echo, 1.5-mm-thick images were more sensitive to VRS in the cerebral convexities than T2-weighted, 5-mm-thick images. The future use of a higher-resolution T2-weighted sequence (512 × 512 × 100 matrix), higher field strength, and thinner sections should improve the visualization and quantification of high-convexity VRS.

We cannot rule out the possibility that the number of enlarged VRS was increased before the onset of the trauma because we did not have access to preinjury brain MR images on any of our patients with TBI. Also, we did not have the opportunity to compare our findings with those of young patients with moderate-to-severe injury, which is associated with a more intense inflammatory response. Undoubtedly, it is important to determine whether the increased number of dilated VRS represents a permanent change and whether it has clinical significance. The average number of VRS did not differ between within days or within several years after injury, and it was not correlated with the elapsed time after head trauma. Although follow-up MR imaging provides a definite answer, the lack of difference between the two groups of patients and the lack of association with time after trauma suggest that perivascular dilation represents a permanent morphologic change. Because histologic correlation was not available in any of our patients, our hypothesis about the etiology of dilated VRS remains speculative. In addition, it is not clear why the imaging findings did not change over time: Both postinflammatory fibrotic changes and shear-strain stretching on the perivascular space might have contributed to the persistence of the increased number of dilated VRS over time. We have started a larger study, including serial clinical, neuropsychological, and MR imaging evaluations, to further explore and elucidate our preliminary findings.

Conclusion

In summary, our results suggest that enlarged high-convexity VRS are a radiologic marker of potential inflammatory changes associated with mild TBI, especially among young subjects. Because the number of VRS is independent of the time of injury, they probably reflect early and permanent brain changes.

References

23. Awad IA, Johnson PC, Spetzler RF, Hodak JA. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly, II: postmortem pathological correlations. *Stroke* 1986;17:1090–1097
We agree with Drs. Bergson, Garg, and Chang that septo-optic dysplasia is a syndrome with a spectrum of abnormalities, both clinically and on MR imaging. The classical clinical triad includes optic nerve hypoplasia, pituitary dysfunction, and agenesis of the septum pellucidum. In our article, we presented 4 children who had hormonal disturbances but no other features of septo-optic dysplasia, apart from a HESX1 mutation in 1 patient. All 4 had an ectopic posterior pituitary lobe, and the periventricular heterotopia was an incidental finding. We postulated that an underlying genetic abnormality, rather than unknown previous trauma, was the most likely explanation for both abnormalities because periventricular heterotopia is known to have a genetic basis in some instances. Furthermore, patients with classical septo-optic dysplasia have been observed with ectopic posterior pituitary lobe and periventricular heterotopia.

In our article, we wished to emphasize the association between the migrational abnormality and ectopic posterior pituitary lobe and the likely genetic basis for both lesions, so patients with classical septo-optic dysplasia were not included. In the setting of classical septo-optic dysplasia, we have observed a patient with a bifrontal malformation of cortical development (Fig 1), periventricular heterotopia, and ectopic posterior pituitary lobe, very similar to the reported case of Bergson, Garg, and Chang. These cases suggest that septo-optic dysplasia encompasses a heterogeneous spectrum of malformations in which specific genetic abnormalities may lead to distinct malformation patterns.

References

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Erratum

In the “Results” section of the abstract and the manuscript the following numbers “(2.4 +/- 2.9, P = .0003)” should have been replaced with “(3.0 +/- 3.0, P = 0.002)”.

Fig 1. Axial T1-weighted inversion recovery (TR/TE/TI, 2448/9/750) image of a 6-year-old boy with septo-optic dysplasia shows right periventricular heterotopia (small arrow) and a bifrontal cortical malformation (arrowheads), very similar to the appearances shown by Bergson, Garg, and Chang. Septal agenesis and ectopic posterior pituitary lobe were also present (not shown).