Severely impaired cerebrovascular reserve in patients with cerebral proliferative angiopathy

Clinical article

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Object. Cerebral proliferative angiopathy (CPA) has been morphologically distinguished from classically appearing brain arteriovenous malformations (AVMs) by exhibition of functional brain parenchyma that is intermingled with abnormal vascular channels. The presence of oligemia in this intralesional brain tissue may suggest ischemia, which is not detected in classic brain AVMs. The authors hypothesized that patients with CPA would exhibit a greater impairment of cerebrovascular reserve in neuronal tissue surrounding the true nidus compared with those with brain AVMs.

Methods. Four patients with CPA, 10 patients with brain AVMs and seizures, and 12 young healthy individuals were studied. The 4 patients with CPA underwent blood oxygen level–dependent MR imaging examinations while applying normoxic step changes in end-tidal CO2 to obtain quantitative cerebrovascular reactivity measurements.

Results. Patients with a CPA lesion exhibited severely impaired perilesional cerebrovascular reserve in comparison with patients with brain AVMs and seizures (0.10 ± 0.03 vs 0.16 ± 0.03, respectively; p < 0.05), and young healthy individuals (0.10 ± 0.03 vs 0.21 ± 0.06, respectively; p < 0.01)

Conclusions. This study demonstrated severely impaired cerebrovascular reserve in the perilesional brain tissue surrounding the abnormal vessels of patients with CPA. This finding may provide an additional means to distinguish CPA from classic brain AVMs. (DOI: 10.3171/2011.6.PED1170)

Key Words • cerebral proliferative angiopathy • cerebrovascular reserve • cerebrovascular reactivity • brain arteriovenous malformation • oligemia • vascular disorders

Cerebral proliferative angiopathy is a rare disease occurring in 3.4% of patients with brain AVMs as reported by Lasjaunias et al.11 Cerebral proliferative angiopathy has been morphologically distinguished from a classic brain AVM by exhibition of functional brain parenchyma, shown histologically,1,11 intermingled with abnormal vascular channels, whereas a classic brain AVM nidus does not contain brain tissue. Furthermore, perfusion-weighted MR imaging studies3,4,17 demonstrate oligemia in the vicinity of the affected vessels, suggesting the presence of ischemia. Such observations imply a management strategy for CPA directed at preventing ischemic changes by improving cortical blood supply, for example by indirect extracranial-intracranial bypass5,10,14 or by creating bur holes.6 This strategy differs from that of brain AVMs, in which management is directed mainly toward preventing hemorrhage. As such, it may be important to be able to distinguish one type of lesion from the other.

Quantitative MR imaging-based mapping of CVR has been used as a surrogate measure of adequate blood supply to brain tissue6,9,12 and for assessment of the cerebrovascular reserve in perinidal brain tissue of classic brain AVMs.7 We hypothesized that CVR would detect a greater impairment of cerebrovascular reserve in neuronal tissue surrounding the true nidus in patients diagnosed with CPA compared with those with brain AVMs.
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Methods

Study Participants

Four patients with CPA were prospectively recruited from the AVM clinic of a single institution (University Health Network, Toronto Western Hospital) over a 6-month period. Reference data from 12 young healthy individuals and from 10 with a classic brain AVM pattern and seizures were retrieved from the database of an ongoing prospective CVR-AVM study using the same study protocol. The study was approved by the local research ethics board, and all patients provided written informed consent prior to participation in the study. There were no adverse events reported during the study.

Features of CPA Lesions

Lasjaunias et al.11 have carefully defined the angioarchitectural features unique to CPA lesions. These features include a large-sized (lobar or even hemispheric) diffuse nidus, absence of a dominant arterial feeder or flow-related aneurysms, near-normal arteriovenous transit time despite the widespread nidus (no shunt identified), no significantly dilated veins, and scattered “puddling” of contrast material in the widespread nidus. Importantly, besides these angioarchitectural criteria, one should consider CPA when brain tissue can be identified between vascular spaces on conventional imaging. Figure 1 in the paper by Lasjaunias et al.11 demonstrates these unique CPA features.

Magnetic Resonance Imaging Protocol and CO2 Delivery

All 4 patients with CPA underwent MR imaging consisting of an anatomical 3D T1-weighted IR-FSPGR acquisition (voxel size 0.86 × 0.86 × 1.0 mm) on a 3-T HDx MR imaging system (Signa, GE Healthcare). Cerebrovascular reactivity was then evaluated using BOLD echo planar gradient echo imaging (TR 2000, TE 30 msec, 3.75 × 3.75 × 5 mm voxels) during normoxic step changes in the end-tidal PCO2 as the vasoactive stimulus. Controlled changes in end-tidal PCO2 were implemented with a custom-built automated gas blender and breathing circuit combination (RespirAct, Thornhill Research, Inc.). The technique applies a method of partial rebreathing to control end-tidal PCO2 and end-tidal partial pressure of O2 independently of each other.16,18 This standardized technique and the protocol have been previously described with reference to a study in patients with brain vascular malformations.7

Data Analysis

Magnetic resonance imaging and end-tidal PCO2 data were imported into the AFNI software.2 The BOLD images were automatically coregistered to the T1-weighted anatomical data set.15 The CVR value was calculated as the percentage change in BOLD signal per mm Hg increase in end-tidal PCO2. Anatomical images and coregistered CVR maps were fitted to a 1-mm isotropic grid to facilitate subsequent analysis. Tissue probability maps were generated from the anatomical images (SPM5; Wellcome Department of Imaging Neuroscience, University College, London) with a threshold at a probability of 0.9 to construct categorical brain tissue masks. The CPA vessels were excluded from the brain tissue masks.

Region of Interest Determination and Statistical Analysis

To construct a 3D ROI containing the CPA vessels, a neuroradiologist manually outlined the abnormal vessels on all slices of the anatomical data set in which the CPA lesion was visible. Best efforts were expended to exclude abnormal CPA vessels such that CVR measurements could be isolated to the intra- and perilesional tissue. For that purpose, the ROI served as a basis for a concentric expansion (rings) by a margin of approximately 2 mm, up to a maximum expansion of 30 mm (Matlab, Image Processing Toolbox; Mathworks). These rings were then combined with the previously generated CPA “mask” to categorize each voxel by tissue class and distance from the CPA lesion. The same analysis was performed again after reflecting the ROI to the contralateral, unaffected hemisphere. Mean CVR was computed for brain tissue for each corresponding successive 2-mm ring up to a region of 30 mm surrounding the lesion. We included two sets of reference data from a previous study: CVR measured in corresponding ROI of young healthy individuals with no history of neurological disease and CVR measured in concentric rings around brain AVMs of seizure-prone patients. The latter group had previously been shown to have impaired cerebrovascular reserve in ringed ROIs surrounding their brain AVMs.7 Cerebrovascular reactivity measurements for each ROI (such as 2 mm, 4 mm, and others) for each of these 3 data sets were compared in the ipsilateral as well as the contralateral hemisphere using the Fisher exact test and Student t-test.

Results

Demographics

We studied 4 patients with CPA (2 males) with an age range of 11–23 years (Fig. 1). Three patients presented with seizures, two of whom had an additional history of intracranial hemorrhage (Table 1). The fourth patient presented with focal neurological deficits. The mean age for the 12 young healthy individuals (6 females) was 37 years (range 20–52 years), and for the 10 patients (4 females) with classic brain AVMs and a history of seizure it was 38 years (range 21–53 years).

Measurements of CVR Around the CPA Lesion

We report CVR values in units of percentage BOLD change per mm Hg increase in end-tidal PCO2 (mean ± SD). Cerebrovascular reactivity in the ipsilateral hemisphere of CPA lesions for all ROIs was reduced compared with reference data from young healthy individuals (0.10 ± 0.03 vs 0.21 ± 0.06, respectively; p < 0.01) and from patients with classic brain AVMs (0.10 ± 0.03 vs 0.16 ± 0.03, respectively; p < 0.05). The CVR was least in ROIs closest to the lesion in patients with CPA and in seizure-prone patients with brain AVMs (Fig. 2A and C).

Cerebrovascular Reactivity Findings in Ipsilateral Versus Contralateral Hemisphere

Comparisons in CVR between the ipsilateral and
The CVR differences show statistical significance up to 30 mm from the lesion. The CVR findings in the contralateral hemisphere are not statistically different from those of the reference data from young healthy individuals (p = 0.67) or from seizure-prone patients with brain AVMs (p = 0.96; Fig. 2B and D). As for patients with seizure and brain AVMs, the CVR findings in the contralateral hemisphere in this data set of patients with CPA also exhibit a CVR pattern within normal boundaries, suggesting that this intra- and perilesional brain tissue is most compromised.

**Discussion**

This study demonstrates severely impaired perilesional cerebrovascular reserve in patients with CPA. This impairment is more pronounced than in seizure-prone patients with classic brain AVMs as previously reported using the same technique (Fig. 2A and C). These CVR findings further support the proposition that CPA is a disease entity that is different from brain AVM.

The impaired CVR in the perilesional tissue in patients diagnosed with CPA suggests that this tissue cannot meet surges in perfusion and may represent a state
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TABLE 1: Patient characteristics and location of CPA lesion

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>CPA Location</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21, F</td>
<td>Lt frontotemporoparietal</td>
<td>seizures &amp; intracranial hemorrhage</td>
</tr>
<tr>
<td>2</td>
<td>23, M</td>
<td>Lt frontotemporal</td>
<td>seizures &amp; intracranial hemorrhage</td>
</tr>
<tr>
<td>3</td>
<td>11, M</td>
<td>Lt frontotemporoparietal</td>
<td>transient neurological deficits</td>
</tr>
<tr>
<td>4</td>
<td>11, F</td>
<td>Lt temporal</td>
<td>seizures</td>
</tr>
</tbody>
</table>

of chronic hypoperfusion, and that brain tissue closest to the CPA is the most compromised. These conclusions are supported by the histological studies from patients with CPA by Chin et al. (who referred to them as “diffuse nidus type AVM”) and by Yaşargil et al. (who called them “holohemispheric AVM”). In addition, angioarchitectural features of CPA are the formation of new blood vessels (angiogenesis) and increased transdural supply, both of which are presumably induced as a response to the chronic or repetitive relative cortical ischemia. As for patients with seizure and brain AVMs, the CVR findings in the contralateral hemisphere in this data set of patients with CPA also exhibits a CVR pattern within normal boundaries, suggesting that this intra- and perilesional brain tissue is most compromised.

Functional neurovascular imaging, in this case BOLD MR imaging acquisitions with a controlled hypercapnic stimulus to assess the cerebrovascular reserve, might provide useful information to identify perilesional ischemic brain tissue that in selected cases may require cerebral revascularization. Surgically created bur holes or indirect extracranial-intracranial bypass improve blood flow to the cortex and have been proposed for treatment of CPA lesions. Postoperative CVR examinations may also be helpful in assessing the efficacy of the revascularization procedure.

Comparison of CVR Results in Different Patient Cohorts

The previously reported impaired perilesional cerebrovascular reserve in seizure-prone patients with brain AVMs has been related to venous congestion, a finding

![Graphs showing cerebrovascular reactivity findings in individual 2-mm ROIs in the ipsilateral and contralateral hemispheres (A and B).](image)

**Fig. 2.** Cerebrovascular reactivity findings in individual 2-mm ROIs in the ipsilateral (A and C) and contralateral (B and D) hemispheres. Cerebrovascular reactivity findings for every individual 2-mm expanded ROI in the ipsilateral and contralateral hemisphere from the CPA lesion for every individual case (gray symbols, A and B) and the combined CVR findings (mean value; gray diamonds, C and D). Reference CVR data from a previous study is represented as a red shaded area for normal range of CVR (A and B) and as a red dotted line (mean of normal CVR; C and D) as measured in 12 healthy young volunteers. The blue dotted line represents the mean CVR of seizure patients with classic brain AVMs.
that was not detected in our cases with CPA. Furthermore, in these 4 patients there appears to be a greater degree of impairment of cerebrovascular reserve distributed in a unique, but consistent pattern. Both groups appear to be commonly prone to seizures, but it is not clear what role, if any, chronic or repetitive hypoperfusion plays in these symptoms.

**Limitations of the Study**

Only 4 patients could be found to establish the study group in this very uncommon disease. However, all 4 showed the same pattern of impaired cerebrovascular reserve. The history of hemorrhage in 2 of the 4 cases does not appear to have influenced the CVR measurement because all 4 showed a similar impairment in cerebrovascular reserve. It is important to note that hemorrhage is not a common presentation in patients with CPA, as opposed to classic brain AVM. The two most frequent symptoms in patients with CPA are seizures and focal neurological deficits. Moreover, the 2 control groups, healthy volunteers and seizure patients with brain AVMs, were sex but not age matched. These control data sets were used retrospectively; the patients with brain AVMs were usually found to present at an older age than patients with CPA. However, this does not necessarily weaken our results, as growing older is associated with a decrease in CVR, whereas in these young patients with CPA, CVR was found to be more impaired.

For comparable CVR measures for the control groups of healthy volunteers and seizure patients with brain AVMs, we used the same imaging protocol and analysis methods, thereby maintaining the maximal 30-mm expansion of the ROI. We realize that the commonly large and widespread CPA lesions may very well expand these borders, resulting in mainly intralesional measures of CVR. This may explain the observations of severely impaired cerebrovascular reserve because intralesional brain tissue in patients with CPA exhibits hypoperfusion.

It is important to note that BOLD MR imaging CVR is not a direct measure of changes in cerebral blood flow. A validation of BOLD MR imaging CVR as an indicator of perfusion changes versus a "gold standard" such as xenon CT has not been reported. However, Mandell et al. verified the technique against arterial spin labeling. Although this technique is also MR imaging-based, it underlies a different principle and the techniques demonstrated good agreement, implying that impaired CVR is related to a decreased cerebral blood flow response, as has been reported for CPA lesions by others.

**Conclusions**

This study demonstrated severely impaired cerebrovascular reserve in the perilesional brain tissue of patients with CPA. This finding may provide an additional means to distinguish CPA from brain AVM.

**Disclosure**

Thornhill Research, Inc., is a for-profit spin-off company of the University of Toronto and the University Health Network charged with commercializing medical devices developed in these institutions. Drs. Fisher and Mikulis retain shares in Thornhill Research, along with the University Health Network, according to the intellectual property policies of the institutions. Author contributions to the study and manuscript preparation include the following. Conception and design: Fierstra, Spieth, Mikulis, Krings. Acquisition of data: Fierstra, Spieth, Tran. Analysis and interpretation of data: Fierstra, Spieth, Conklin. Drafting the article: Fierstra, Spieth, Krings. Critically revising the article: All authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Fierstra. Statistical analysis: Conklin. Administrative/technical/material support: Tran, Tymianski, ter Brugge, Fisher, Mikulis, Krings. Study supervision: Tymianski, ter Brugge, Fisher, Mikulis, Krings.

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