Cerebral Proliferative Angiopathy
Clinical and Angiographic Description of an Entity Different From Cerebral AVMs

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Background and Purpose—The purpose of this article is to describe “cerebral proliferative angiopathy” (CPA) as a clinical entity, which may be regarded as separate from “classical” brain AVMs in angioarchitecture, natural history, clinical presentation, and, therefore, treatment and which can be discerned from other cerebral AVMs by characteristic imaging features.

Methods—In a prospectively entered databank encompassing 1434 patients with brain AVMs, a subgroup of 49 patients harboring specific angiographic characteristics were identified. Their charts and imaging films were retrospectively reviewed.

Results—We found a preponderance of CPA in young (mean age: 22) females (67%). Clinical symptoms were seizures, disabling headaches, and stroke-like symptoms; hemorrhagic presentations were exceptional. On cross-sectional imaging, CPA demonstrated as a diffuse network of densely enhancing vascular spaces with intermingled normal brain parenchyma. The discrepancy between the large size of the nidus and the small shunting volume, the absence of flow-related aneurysms, the presence of diffuse angiogenesis (eg, transdural supply, progressive arterial occlusion), and the small calibre of a multitude of feeding arteries and draining veins were the angiographic hallmarks of this disease.

Conclusion—The diffuse angiogenetic activity is presumably related to reduced perinidal perfusion and subsequent chronic cortical ischemia. Natural history demonstrates a low risk of hemorrhage. CPA may be regarded as a separate clinical entity different to “classical” cerebral AVMs, because normal brain is interspersed with the abnormal vascular channels increasing the risk of neurological deficit in aggressive treatments, which in the light of the natural history does not seem to be indicated. (Stroke. 2008;39:878-885.)

Key Words: arteriovenous malformation ■ ischemia ■ angiogenesis ■ embolization ■ angiopathy

Basic classifications of vascular diseases optimally use angiomorphological, pathological, biological, and clinical data. However, in the case of brain arteriovenous malformation, the most often encountered classifications are based on the topography (eloquence of the involved brain), the size of the nidus, the type of venous drainage, and pathological specimen. This type of classifications tends to focus solely on the difficulty for interventional assessment of the lesion, rather than on an understanding of the disease. Using this classification therefore does not enable the neurovascular specialist to further subclassify the (possibly) heterogeneous group of brain AVMs. This distinction is not only of academic interest, but may also have clinical consequences because different types of brain AVMs may have different natural histories, different responses to treatments and therefore different therapeutic indications.

Over the course of the last 30 years our group has been involved in the clinical assessment and endovascular treatment of brain AVMs in adults and children. In a prospective fashion, we entered clinical, angiomorphological, and CT/MR imaging data of all patients undergoing cerebral angiography in a dedicated interventional databank that allowed us to retrospectively review specific imaging appearances in patients harboring a brain AVM.

The purpose of this article is to describe a clinical entity, which must be regarded as separate from “classical” brain AVMs in angioarchitecture, natural history, clinical presentation, and, therefore, treatment. It can be distinguished from...
“classical” AVMs by specific characteristic clinical and imaging features.

Methods

Eight years after starting to treat cerebral AVM, when constituting our final interventional databank in 1989, we introduced the term “cerebral proliferative angiopathy” (CPA) as a presumed diagnosis for a peculiar type of large brain arteriovenous malformations (AVMs) that demonstrated distinctive angiogenetic activity by which they could be separated from “classical” brain AVMs. This denomination was strictly based on angiographic evidence of nonfocal angiogenetic activity, ie, the presence of transdural supply and stenoses of feeding arteries. Other distinctive features were the absence of dominant feeders to a large nidus (often lobar or even hemispheric), the small size of the draining veins in relation to the size of the arteriovenous shunting zone, the presence of intermingled brain between the vascular spaces as demonstrated by MRI, and the above mentioned transdural supply and presence of proximal arterial stenoses. Within this databank, to date (May 2006), there is a total of 4058 patients, of which 1434 patients harbor a nongalenic brain AVM. Based on the above mentioned angiomorphological criteria, a total of 49 patients were entered as harboring a CPA. In all patients, age, sex, seizure activity, presence and frequency of intracranial hemorrhage, incidence of other neurological symptoms, and deficits were entered. In all patients biplane subtraction angiographies, CT or MRI were available for retrospective image evaluation. Advanced imaging techniques (MR perfusion measurements) were available in 7 patients. All imaging, demographic, and clinical data were reviewed and evaluated concerning the characteristics described in the Table. A pathological specimen was available in 1 patient who died from an intracerebral hemorrhage. Paraffin-embedded tissues were stained with hemotoxylin and eosin (HE), orceine van Giesen (elastic tissue), Gordon Sweet (Collagen Type III=Reticulin), and Masson trichrome (Collagen Type I) for pathological examination. Treatment modalities of the CPA, if performed, and clinical outcome/follow-up were also entered into the databank and evaluated accordingly.

Results

Epidemiology

CPA was diagnosed in 3.4% (49 of 1434) brain arteriovenous malformations. Of the 49 patients diagnosed as “cerebral proliferative angiopathy,” there were 33 females (67%), compared with 48% females in the overall AVM population (669/1434=49). Fisher exact test revealed a value of \( P=0.005 \). Mean age at symptom onset (or, if asymptomatic, at diagnosis) was 22 years with a median of 17.5 years (range: 10 to 65 years) which demonstrated no statistically significant difference to our overall AVM patient population (that is, however, biased as Bicêtre is a neuropaedia endovascular referral center).

Clinical Aspects

In 22 patients (45%), seizures constituted the presenting symptom (in contrast to 215/1385=16% in the overall AVM population, Fisher \( P<0.001 \)), severe, in some cases even disabling headaches were present in 20 patients (41%) (compared with 195/1385=14% in the overall AVM population; Fisher \( P<0.001 \)). Six patients (12%) had hemorrhagic events (in contrast to 583/1385=42% in the overall AVM population, Fisher \( P<0.001 \)); in 2 patients a single hemorrhage occurred before treatment; in the remaining 4 patients, recurrent hemorrhages were present (67%). One patient died of one of these recurring hemorrhages. In comparison, only 24 of 583 (4%) patients in our overall AVM population had a rehemorrhage (Fisher \( P<0.001 \)). Stroke-like symptoms, transitory ischemic attacks (TIAs), or neurological deficits not owing to a hemorrhage were present in 8 patients with CPA (16%) (compared with 24/1385=2%, in the overall AVM population Fisher \( P<0.001 \); 1 patient each had venous congestion and a hydrocephalus.

Cross-Sectional Imaging Characteristics

On MRI and CT (which was available in all patients), CPA presented as a diffuse network of densely enhancing vascular spaces with intermingled normal brain parenchyma in all 49 patients (Figure 1). Small disperse flow voids could be seen on T2 and T1 weighted images that in some patients covered the whole hemisphere or multiple lobes. The right hemisphere was affected in 22 patients, both hemispheres were affected in 2 patients (both patients presented with infratentorial, vermian CPAs). The lobes were affected as follows: frontal lobe, 20; temporal lobe, 24; parietal lobe, 19; occipital lobe, 12; the infratentorial brain was affected in 11 cases. In 14 patients, CPA was present in a single lobe, in the majority of patients 2 or more lobes were affected. The lesion extended to the basal ganglia and thalamus in 42 cases (85%), pure superficial localizations were rare (7 patients, 14%). In the majority

| Table. Demographical, Angiomorphological, and Clinical Data Reviewed |
|------------------|------------------|
| **Demographics** | Age/ Sex         |
| **Angiomorphological features** | **Proximal arteries** |
| Dominant feeder present/absent | Multiple feeders? |
| Proximal artery stenosis | Proximal aneurysm |
| Transdural arteries | Supplying the nidus present/absent |
| Supplying normal brain tissue present/absent | Nidus |
| Size (<3, 3–6, >6 cm) | Type (circumscribed vs fuzzy limits) |
| Capillary angioectasia present/absent | Localization (lobar vs multilobar; superficial vs deep, uni- vs bilateral, Within a watershed-zone) |
| Draining veins | Early venous filling (present/absent) |
| Enlarged draining veins (present/absent) | MR/CT imaging features |
| Venous congestion present/absent | Intermingled normal brain present/absent |
| MR perfusion | Clinical Data |
| Seizures | Headaches |
| Hemorrhage (no, single, multiple) | Neurological deficits |

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of cases (33/49=67%), the localization was in between different vascular territories (so called watershed zone).

Compared with the size of the nidus, there was paucity of draining vessels seen on MRI or CT, these were often only moderately enlarged (Figure 2). Perfusion-weighted MRI (PWI) was available in 7 patients and demonstrated that perfusion abnormalities extended far beyond the boundaries of the morphological abnormalities seen on conventional MR
sequences, indicating the presence of a disease affecting the whole hemisphere. Within the morphologically identifiable nidus an increased cerebral blood volumen and an only slightly decreased TTP (time to peak) and a prolonged mean transit time (MTT) were present (Figure 3). Remote from the nidus, in both cortical and subcortical areas that were normal on conventional MRI, increased TTP values and a decreased blood volumen were present which were indicative of remote and widespread hypoperfusion. Evidence of acute ischemia (diffusion-weighted MRI) was not found.

**Angiomorphology**

Angiography revealed absence of dominant feeders in all cases, instead the CPA was fed by multiple arteries that were not or moderately enlarged, all arteries of the affected region seemed to contribute equally to the malformation (Figure 4). Stenoses of the proximal arteries (ie, ICA, M1, A1 segment) were present in 19 patients (39%) (Figures 5 and 6), whereas proximal aneurysms were present in 6 cases (12%). Transdural supply was encountered in 29 patients (59%); in 20 of them, this transdural supply was aimed not only at the malformation but also at normal brain tissue (Figure 4). The nidus had a classical appearance with scattered “puddling” of contrast which persisted into the late arterial and early venous phase within what seemed like capillary ectasias (Figure 1). The diameter of the nidus was between 3 and 6 cm in 29 patients and more than 6 cm in 20 cases. In the majority of
In 46/49 cases, the nidus had a fuzzy appearance and was not well circumscribed. Intranidal vessels showed a capillary angioectatic aspect in 43 patients (88%), perinidal angiogenesis was present in 24 (49%) patients and difficult to distinguish from the nidus proper (Figures 2 and 5). There was a large area of rapid arteriovenous transit (shunting zone) but no high-flow arteriovenous fistulous aspect in any patient. No flow-related aneurysms were encountered in any patients despite the size of the lesion. In those cases where the contrast demonstrated a more rapid capillary venous filling (13 patients 27%), the veins were slightly enlarged; however, early opacification of the veins was the exception rather than the rule. In no case, the size of the draining veins, the “shunting volume,” and the time until the veins were visualized “corresponded” to the size of the nidus. Angiographic signs of venous congestion ie, delayed drainage of the nonaffected brain (presumably attributable to the increased cerebral blood volume) were present in 9 patients (18%). Either angiogenesis remote from the affected zone (ie, transdural supply to brain areas not affected by the disease), and centripetal stenosis testified for the “proliferative” aspect of the disease in all patients.

Pathology

A pathological specimen was available in 1 patient and showed abnormal arteries and veins with altered lamination of the internal elastic lamina and muscle fibers on the arterial site and collagenous thickening of the veins. Type IV collagen was expressed intensely in the subendothelium. The most striking feature was the presence of normal appearing

Figure 5. Fifteen-year-old boy with epilepsy. Angiography of the right ICA in the arterial and venous phase (A, B: lateral views, C, D: frontal views), MRI (T1-weighted precontrast, frames E and F), and frontal views of the left ICA (frame G) and right vertebral artery (frame H) reveal a fuzzy appearing nidus with interspersed brain in the left basal ganglia, a mild stenosis of the right distal ICA, and diffuse neoangiogenesis in the parietooccipital areas. Within the nidus angioectasias are present. The venous drainage is slightly too early, however no areas of high-flow shunting can be perceived.

Figure 6. Two different patients with right frontoparietal proliferative angiopathy with similar stenoses on the proximal M1 segment (arrows).
neural tissue intermingled between these vascular channels, whereas perivascular gliosis was only mild, with additional capillarogenesis within the subcortical region (Figure 7).

**Treatment Options**

Treatment indications were, because of the specific histological characteristics of this disease, set very strictly and confined to hemorrhage, identifiable fragile angioarchitecture (such as intranidal aneurysmal ectasias), uncontrollable seizures, and disabling headaches. The clinical manifestations and functional MRI were also pointing to the ischemic nature of the symptoms either via classic venous congestion in the immediate vicinity of the lesion or arterial deprivation majorly by the proximal stenotic changes. Therefore, treatment (partial targeted embolization employing glue, preferably in non-eloquent areas) was only performed in 23 of the reported 49 patients. In 2 of the treated patients, new neurological deficits occurred presumably owing to the presence of normal neurological tissue interspersed with the embolized vessels. In view of the arterial ischemic nature of the brain tissue suffering at the level of the shunting zone, calvarial burrhole treatment was performed in 2 patients in which spontaneous transdural supply was poor. Eleven (untreated) patients were lost to follow-up; in the remaining 38 patients we have a total follow-up of 145 patient years (mean: 3 years, range: 1 to 12 years). After therapy, improvement of headaches and seizure control was achieved in 16 cases, 6 patients remained clinically stable, and 1 patient deteriorated (persistent neurological deficit following embolization with new cerebellar symptoms). Hemorrhagic events could be controlled in those 6 patients that presented with hemorrhage. Both patients treated with burrholes demonstrated a dramatic and persisting improvement of their symptoms (disabling headaches that have disappeared after treatment, follow-up: 2 and 5 years, respectively).

**Discussion**

The entity described in this manuscript differs from other arteriovenous malformations in their angiomorphology, histology, presumed pathomechanism, epidemiology, natural history, and clinical presentation, and may therefore be classified as a group separate of AVMs.

The salient issues of CPA which helps to discern it from “classical” brain AVMs are from an angiomorphological standpoint: the absence of dominant feeders or flow-related aneurysms, the presence of proximal stenoses on the feeding arteries, the extensive transdural supply to both healthy and pathological tissues, the large size (which might be lobar or even hemispheric), the presence of capillary angioectasias and the only moderately enlarged veins (compared with the size of the nidus) as described extensively in the Results section. Moreover, this special entity of false brain AVM can be suspected when on conventional imaging, brain tissue is intermingled between the vascular spaces. Perfusion-weighted MRI was indicative of an increased blood volume within the nidus with an increase mean transit time indicative of capillary and venous ectasias and an area of hypoperfusion that could be seen throughout the affected hemisphere. This differs from classical brain AVMs where the MTT is decreased indicative of a shunt and the perinidal areas are not as severely hypoperfused as present in PA. This hypoperfusion trigger might then lead to an uncontrolled angiogenic
response. Whereas transdural supply after iatrogenic ischemia is a normal response to an abnormal demand, the transdural supply in PA is an abnormal response to an abnormal demand.

Histopathological Features
On histopathology, "classical" cerebral arteriovenous malformations consist of a tangle of abnormal arteries and veins without an intervening capillary bed. In between the abnormal vascular channels, gliotic and nonfunctional parenchyma may be present. In the feeding arteries, the usual lamination of elastic and muscle fibers is altered, the internal elastic lamina may be reduplicated, interrupted or distorted, arterial muscle fibers may be focally increased or might be thinned to form arterial aneurysms. Thickening of veins attributable to collagenous tissue are typical. Secondary degenerations such as fibrosis, atheromas, and calcifications may appear. The surrounding cortex shows a loss of neurons accompanied by an increase in fibrillary glia. Former neural tissue between the abnormal blood vessels is restricted to thin gliotic bands, there are no identifiable neurons present. Signs of prior hemorrhage (macrophages containing iron pigment) might be present. Although blood vessels, both on the venous and arterial site, were similar to those found in classical brain AVMs, the major difference was the presence of identifiable neurons and normal brain tissue between the abnormal vessels in our specimen of proliferative angiopathy and on the MRI performed. This implies that the brain tissue within the "nidus" of the CPA is functional, similar to brain tissue found in between the abnormal vascular channels present in capillary telangiectasias. In this regard, CPA is a disease similar to some of the cases that Chin described as "diffuse nidus" AVM and that other authors referred to as "holohemispheric giant AVM." In their series of 12 patients, Chin et al report on the surgical treatment with subsequent histological evaluation of the excised specimen. Similar to our histology and our structural MRI findings (which were not available in the majority of patients in the series reported by Chin), they found normal brain parenchyma interspersed with vascular channels.

The Proliferative Aspect
We chose the term "proliferative" angiopathy because there are several features of the disease that strongly suggest the formation of new blood vessels in this disease (which is also different from classical AVMs). This proliferative component is testified by the meningeal contribution to the lesion and to healthy brain tissue by transdural supply demonstrated bilaterally, anywhere on the cortex and sometimes infra- and supratentorially. The observed angiogenesis is presumably induced as a response to the (relative) cortical ischemia (with unknown signaling media) that was demonstrated with PWI and that is neither related to a previous hemorrhagic event nor to an increased risk of hemorrhage in the future (because these arteries have a different origin compared with "classical" dural arteriovenous shunts). Instead, our results indicate an increased risk of rebleeding once a hemorrhage has occurred. This may be an expression of the increased vulnerability of the newly formed vessels produced at a high proliferation rate. Segmental stenosis of the proximal middle or anterior cerebral arteries can be seen during follow up. The coexistence of angioectasias and stenoses implies a problem of vessel wall proliferation as a possible underlying pathomechanism of this disease. When considering flow on one hand and angiogenetic response on the other, CPA can be regarded as an intermediate or transition between the 2 major types of vascular lesions defined in the biological classification of vascular lesions in childhood and infancy by Mulliken and Glowacki in 1975. In their classification, these authors differentiated between 2 major types of vascular lesions: lesions that demonstrate cellular proliferation and endothelial hyperplasia ("hemangiomas" or true vascular tumors) and those with normal endothelial turnover but with true structural abnormalities of the capillary, venous, lymphatic or arterial channel (vascular malformations). Although brain AVMs (where the flow is remarkably increased while active angiogenesis is not present) belong to the latter group, hemangiomas (as present in the PHACES syndrome, where no arteriovenous shunts but a prominent proliferative element are encountered) belong to the former. Proliferative angiopathy exhibits features of both vascular lesion types with a malformative aspect (that is however less pronounced compared with true AVMs) and a proliferative aspect (that is, again less prominent compared with hemangiomas).

Clinical Features
When evaluating patients with angiomorphological features suggestive of CPA we demonstrated that they had a significantly different clinical presentation and clinical course compared with classical brain AVMs. Patients (typically, young females 2:1) usually do not present with an acute neurological deficit or hemorrhage but more commonly with epileptic manifestations, headaches, and progressive neurological deficits.

It is interesting to note that in the multifactorial analysis of angioarchitectural features in relation to the hemorrhagic risk, the association of arterial stenoses with angiogenesis was the only one to negatively affect the risk of hemorrhage. Because in this analysis, however, cases of CPA are included, we suspect that the natural history of these more benign lesions has affected the analysis.

Once a bleeding had occurred, however, the chances of rebleeding were in this small group of patients higher than in the group of normal brain AVMs. Although a referral bias cannot completely be excluded as a potential source of these peculiarities, their high statistical significance as outlined in the results is an argument for a differing clinical course.

Other particular features are the high rate of stroke-like symptoms, TIAs, and neurological defects not owing to a hemorrhage that suit the assumption that CPA is a disease related to ischemia rather than hemorrhage. Seizures and disabling headaches, which occurred significantly more often in the CPA population compared with the AVM population studied by our group may also, at least in part be explained by the hemodynamic dysregulation.

Implications for Treatment
Once this pathological entity is diagnosed, treatment should be adopted to its specific characteristics. Surgery and radio-
surgery carry the risk of permanent neurological deficit attributable to the interspersed normal neural tissue. Similarly, large nontargeted embolization of these malformations carries a larger risk of neurological deficits, because normal brain tissue may be embolized.16 These kinds of treatment should therefore be reserved to patients with otherwise intractable headaches and epilepsy. In our series, even partial treatment led to a sufficient control of the symptoms in the majority of selected patients. Based on our follow-up observations and the relatively large number of patients with CPA, it is not apparent that this disease carries a high risk of hemorrhage. Our findings do not support complete eradication of this type of malformation is desirable or even appropriate. Because one of the major pathomechanisms of this disease is ischemia (which in itself is probably multifactorial owing to incompetent angiogenesis, “steal” phenomenon, arterial stenosis, and capillary wall involvement) a therapy that enhances cortical blood supply can be indicated. In our series, we used calvarial burrholes in 2 patients with very good results concerning their symptomatology with a follow-up of now 3 and 5 years, respectively. Similar to Moya-Moya-like diseases these burrholes increased the cortical blood supply by recruiting additional dural blood supply. If patients, however, present with hemorrhage, endovascular treatment should be performed and aimed at “fragile” areas that may be identified during angiography.27

Conclusion
In proliferative angiopathy, although seizures are the most common clinical symptom at presentation, headaches and progressive deficits are also possible whereas hemorrhage is exceptional. In our experience the risk of hemorrhage is low at presentation, however the risk of recurrence, once a hemorrhagic episode has occurred, seems to be high. Transdural supply in remote locations (supra and infra tentorial, bilateral) can suggest the diffuse character of the angiogenetic activity of the disease, suggesting unrepressed response to cerebral subischemic manifestations. Proliferative angiopathy may be confused with true cerebral AVMs and thought to represent a diffuse nidus. Proper recognition and classification is important, as it identifies the presence of normal brain tissue intermingled with the vascular spaces. Primary treatment should therefore not be embolization (nor surgery, nor radiation therapy) unless areas of the angioarchitecture suggest zones of weakness or demonstrate obvious constraints to the eloquent brain. Headaches are often dramatically alleviated by a partial and limited arterial embolization in noneloquent areas, without treatment of the dural component. Localized forms of proliferative angiopathy can be seen in children; they probably develop at an older age, because they are not associated with mental retardation or local cerebral atrophy. Perfusion MRI has reinforced the suspicion of chronic ischemic disease with angiogenetic activity as in moyamoya, and similar treatment with burrholes has been successfully performed in some cases with immediate good clinical results on both the headaches and the seizure response to medical treatment.

Disclosures
None.

References
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