Perianeurysmal edema in giant intracranial aneurysms in relation to aneurysm location, size, and partial thrombosis

Julius Dengler, MD,¹ Nicolai Maldaner,¹ Philippe Bijlenga, MD, PhD,² Jan-Karl Burkhardt, MD,³ Alexander Graewe, MD,⁴ Susanne Guhl, MD,⁵ Bujung Hong, MD,⁶ Christian Hohaus, MD,⁷ Adisa Kursumovic, MD,⁸ Dorothee Mielke, MD,⁹ Karl-Michael Schebesch, MD,¹⁰ Maria Wostrack, MD,¹¹ Daniel Rufenacht, MD,¹² Peter Vajkoczy, MD,¹ and Nils Ole Schmidt, MD,¹³ on behalf of the Giant Intracranial Aneurysm Study Group

¹Department of Neurosurgery, Charité-Universitätsmedizin Berlin; ⁴Department of Neurosurgery, Unfallkrankenhaus Berlin; ⁵Department of Neurosurgery, University of Greifswald; ⁶Department of Neurosurgery, Hannover Medical School, Hannover; ⁷Department of Neurosurgery, BG Hospital Bergmannstrasse, Halle; ⁸Department of Neurosurgery and Interventional Neuroradiology, Klinikum Deggendorf; ⁹Department of Neurosurgery, Georg-August-University Göttingen; ¹⁰Department of Neurosurgery, University of Regensburg; ¹¹Department of Neurosurgery, Technical University of Munich; ¹³Department of Neurosurgery, University Medical Center, Hamburg Eppendorf, Germany; ¹²Zentrum fuer Neuroradiologie, Clinic Hirslanden, Zurich; ²Service de Neurochirurgie, Faculté de Médecine de Genève and Hôpitaux Universitaires de Genève; and ³Department of Neurosurgery, University Hospital of Zurich, Switzerland

OBJECT The underlying mechanisms causing intracranial perianeurysmal edema (PAE) are still poorly understood. Since PAE is most frequently observed in giant intracranial aneurysms (GIAs), the authors designed a study to examine the occurrence of PAE in relation to the location, size, and partial thrombosis (PT) of GIAs along with the clinical impact of PAE.

METHODS Magnetic resonance imaging data for patients with a diagnosis of unruptured GIA from the international multicenter Giant Intracranial Aneurysm Registry were retrospectively analyzed with regard to location and size of the GIA, PAE volume, and the presence of PT. The occurrence of PAE was correlated to clinical findings.

RESULTS Imaging data for 69 GIAs were eligible for inclusion in this study. Perianeurysmal edema was observed in 33.3% of all cases, with the highest frequency in GIAs of the middle cerebral artery (MCA; 68.8%) and the lowest frequency in GIAs of the cavernous internal carotid artery (ICA; 0.0%). Independent predictors of PAE formation were GIA volume (OR 1.13, $p = 0.02$) and the occurrence of PT (OR 9.84, $p = 0.04$). Giant intracranial aneurysm location did not predict PAE occurrence. Giant aneurysms with PAE were larger than GIAs without PAE ($p < 0.01$), and GIA volume correlated with PAE volume ($r_s = 0.51$, $p = 0.01$). Perianeurysmal edema had no influence on the modified Rankin Scale score ($p = 0.30$ or the occurrence of aphasia ($p = 0.61$) or hemiparesis ($p = 0.82$).

CONCLUSIONS Perianeurysmal edema was associated with GIA size and the presence of PT. As no PAE was observed in cavernous ICA aneurysms, even though they exerted mass effect on the brain and also displayed PT, the dura mater may serve as a barrier protecting the brain from PAE formation.

Clinical trial registration no.: NCT02066493 (clinicaltrials.gov)

<http://thejns.org/doi/abs/10.3171/2014.10.JNS141560>

KEY WORDS giant intracranial aneurysm; aneurysm volume; perianeurysmal edema; partially thrombosed aneurysm; vascular disorders

ABBREVIATIONS ACA = anterior cerebral artery; GIA = giant intracranial aneurysm; ICA = internal carotid artery; ICH = intracerebral hemorrhage; MCA = middle cerebral artery; mRS = modified Rankin Scale; PAE = perianeurysmal edema; PT = partial thrombosis.

SUBMITTED July 3, 2014. **ACCEPTED** October 16, 2014.

INCLUDE WHEN CITING Published online April 17, 2015; DOI: 10.3171/2014.10.JNS141560.

DISCLOSURE The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. The Giant Intracranial Aneurysm Registry is funded by the Center for Stroke Research-Berlin (Grant No. CS-2009-12) to Dr. Dengler, the coordinating officer of the registry. This financial support exclusively funds the maintenance of the internet-based database.

ABOUT 5% of all intracranial aneurysms display a diameter of at least 25 mm and are therefore termed “giant intracranial aneurysms” (GIAs).¹⁷ Because of the dismal natural history of these lesions, both surgical and endovascular treatment strategies are increasingly entering the clinical routine, yet treatment-associated morbidity is described as significantly higher than that for smaller intracranial aneurysms.¹⁷ Similar to brain tumors or intracerebral hemorrhage (ICH), GIAs usually exert considerable mass effect on the brain, which can cause shifts of brain matter with subsequent neurological deficits. This GIA-related mass effect can be associated with perianeurysmal edema (PAE), which is believed to aggravate the patient’s condition and increase treatment morbidity.^{5,6} While perilesional edema is frequent in brain tumors or ICH and therefore well studied, PAE is a rare phenomenon and its origins have yet to be systematically examined.^{14,18} In ICH, perilesional edema was shown to be associated with increasing mass effect caused by the hemorrhage and the formation of a thrombus at the border between the ICH and brain parenchyma.¹⁸ As mass effect and partial thrombosis (PT) are more frequently observed in GIAs than in smaller aneurysms, a systematic examination of GIA may improve our understanding of how PAE evolves.⁸

Therefore, we designed a retrospective multicenter study using imaging and clinical data from patients included in the international multicenter Giant Intracranial Aneurysm Registry to examine the prevalence of PAE in relation to the location, size, and PT of an unruptured GIA.³ We also aimed to describe whether the occurrence of PAE in GIA affects a patient’s clinical condition.

Methods

The study presented here is based on a retrospective analysis of the GIA registry imaging library. The GIA registry was initiated as an international platform to collect both clinical and imaging data exclusively on GIA (see *Appendix* for a list of members of the Giant Intracranial Aneurysm Study Group).³ It was approved by the ethics committee of its coordinating center at the Charité, Berlin, and by the ethics committee for each participating center. All patients consented to participate in the registry. The GIA registry is funded by the Center for Stroke Research-Berlin and is registered with the ClinicalTrials.gov database (<http://clinicaltrials.gov>) and its registration no. is NCT02066493.

Patients

Patients were eligible for this retrospective analysis if they were registered in the GIA registry with a diagnosis of unruptured GIA, defined as an intracranial aneurysm measuring ≥ 25 mm in diameter.¹⁷ Moreover, preinterventional MRI had to be available in the registry’s imaging database. Since transmission of imaging data is not mandatory for the inclusion of cases in the GIA registry, the number of cases examined in the specific study presented here differs from the total number of cases currently contained in the registry.

Giant Intracranial Aneurysm Characteristics

A GIA diameter ≥ 25 mm had to be verified using both angiography (digital subtraction, CT, or MR) and a 3D imaging technique (CT or MRI). Thrombosed parts of the aneurysm and the aneurysm wall counted as part of the aneurysm when measuring diameters and volumes. The vascular origin of the GIA was described using the following categories: anterior cerebral artery (ACA; including the anterior communicating artery), middle cerebral artery (MCA), and posterior circulation (including vertebral, basilar, cerebellar, and posterior cerebral arteries). Giant intracranial aneurysms of the internal carotid artery (ICA) were categorized into 2 groups: cavernous ICA aneurysms (comprising extradural GIAs located within the cavernous sinus and those in the transitional zone, which originate between both dural rings but do not enter the subarachnoid space) and supraclinoid ICA aneurysms (comprising all subarachnoid ICA aneurysms above the transitional zone along with posterior communicating artery aneurysms).

Mass effect was defined as any sign of displacement of the brain parenchyma from its anatomically normal position, caused by the GIA. The location of this mass effect was described using the cerebral lobes or brain regions affected by it, divided into the following categories: frontal, frontotemporal (for simultaneous mass effect on the frontal and temporal lobes), temporomesial, temporal (including temporo-polar and temporo-central), temporo-lateral, parietal, insular, cerebellar, or brainstem.

Partial thrombosis was defined as a difference between the perfused GIA volume as seen on angiography and the GIA volume on MRI. Partial thrombosis was documented independent of whether the thrombus was located intraluminally, adherent to the GIA wall, or partially integrated into the GIA wall. Perianeurysmal edema was defined, in accordance with previously published work, as a region of hyperintensity on T2-weighted images in the vicinity of the GIA.^{2,12} If diffusion-weighted MRI with apparent diffusion coefficient (ADC) mapping showed confluent areas of ischemia within such a region, it was not defined as PAE. Relative PAE volume was defined as the ratio of PAE volume/GIA volume with values > 1 indicating that the PAE was larger and values < 1 indicating that the PAE was smaller than the GIA.

Giant Intracranial Aneurysm Volumetry

As brain tumors and ICHs are routinely quantified using their volume, all GIAs were subjected to volumetry using the software iPlan Cranial (BrainLab). Two experienced examiners (J.D. and N.M.) from the GIA registry coordinating center independently conducted all measurements using T2-weighted imaging. The circumference of the GIAs and their PAE were marked manually using the mouse cursor within each slice of the T2-weighted images. The software then calculated the volumes by multiplying the marked areas in each slice with the slice thickness.

Clinical Characteristics

Clinical characteristics for each patient were extracted from the GIA registry database. They included the modi-

fied Rankin Scale (mRS) score and the presence of aphasia or hemiparesis as potential signs of mass effect.

Statistical Analysis

As GIA volume and PAE volume were measured by 2 separate examiners, interobserver agreement was examined using the 2-way random-effects model intraclass correlation test. All variables were analyzed for normal distribution using the Shapiro-Wilk test. Since the variables relevant for this study were not distributed normally, their values are given as medians with 95% confidence intervals, unless stated otherwise. A binary logistic regression model, which included PAE as the dependent variable and GIA volume, the occurrence of PT, and GIA location (both vessel of origin and location of mass effect) as independent variables, was used to calculate the odds ratios for potential associations. The Kruskal-Wallis test was used to compare volumes in relation to different locations for the entire patient cohort. The Mann-Whitney U-test was used to compare values between 2 specific locations. The relation between GIA volume and PAE volume was examined using the Spearman correlation. The chi-square test was applied to evaluate the relation between the presence of PAE and aphasia or hemiparesis. Ordinal regression analysis was used to examine an association between the presence of PAE and the mRS score. All statistical analyses were conducted using SPSS software, version 22.0.0.0 (IBM Corp.).

Results

Magnetic resonance imaging data for 69 unruptured GIAs in 66 patients were collected in the GIA registry imaging database between January 2009 and November 2013 at 12 participating centers. All of these cases were included in this study. Magnetic resonance imaging data were available with a mean axial slice thickness of 3.4 mm (SD 1.6). Interobserver agreement was excellent for GIA volume and PAE volume (each with correlation coefficients > 0.92 , $p < 0.05$). Patient and aneurysm characteristics are listed in Table 1.

Prevalence and Independent Predictors of PAE

Among the entire cohort of 69 unruptured GIAs, 23 GIAs were associated with PAE, resulting in an overall prevalence of 33.3% GIA-associated PAE. Binary regression analysis showed that GIA volume (OR 1.13, 95% CI 1.02–1.25, $p = 0.02$) and the occurrence of PT (OR 9.84, 95% CI 1.16–83.73, $p = 0.04$) were independent predictors of PAE formation. Giant intracranial aneurysm location did not predict PAE occurrence, with p values of 0.64 for the vessel origin and 0.87 for the location of mass effect.

Perianeurysmal Edema and GIA Location

Figure 1 left shows that the highest proportion of PAE was observed in GIAs of the MCA at 66.7%, followed by GIAs of the posterior circulation at 46.7% and of the supraclinoid ICA at 33.3%. No PAE was observed in GIAs of the cavernous ICA. We also examined the proportion of PAE in relation to the location of GIA-induced mass effect (Fig. 1 right). We observed the highest proportions of PAE

TABLE 1. Summary of patient and aneurysm characteristics

Characteristic	Entire Cohort	No PAE	PAE
Mean age in yrs (SD)	56.4 (14.1)	55.8 (14.7)	57.7 (12.9)
Patient sex (F/M)	38/31	30/16	8/15
No. of GIAs (%)	69	46 (66.7)	23 (33.3)
GIA location			
ACA	6	4	2
Cavernous ICA	23	23	0
Supraclinoid ICA	7	5	2
MCA	18	6	12
Posterior circulation	15	8	7
Medain GIA vol in cm ³ (IQR)	9.3 (7.3)	8.1 (6.1)	14.1 (17.4)
Proportion of GIA w/ PT (%)	47/69 (68.1)	25/46 (54.4)	22/23 (95.7)

IQR = interquartile range; SD = standard deviation.

when mass effect was present in a frontotemporal location and at the brainstem, whereas no PAE was observed in GIAs exerting temporomesial mass effect.

To understand the relationship between the vessel origin of the GIA and the location of its mass effect, we co-localized both variables (Fig. 2): while frontal, frontotemporal, and temporal mass effects were caused by GIAs of different vascular origins, temporomesial mass effect was exclusively caused by GIAs of the cavernous ICA. Mass effect on the brainstem was caused exclusively by GIAs of the posterior circulation, which were all vertebrobasilar or basilar artery GIAs.

Perianeurysmal Edema and GIA Volume

Since GIA volume was identified as an independent predictor of PAE occurrence in our patient cohort, we examined GIA volume in more detail. We found that volumes of GIAs with PAE were significantly larger than volumes of GIAs without PAE ($p < 0.01$; Fig. 3). Four subgroups (MCA, posterior circulation, frontotemporal, and brainstem) had large enough case numbers for separate analyses. In GIAs of the MCA, we found a significant difference in volume between GIAs with and those without PAE ($p = 0.01$). At the other aneurysm locations, there was a trend toward larger GIA volumes if PAE was present, but this trend did not reach statistical significance.

Perianeurysmal Edema Volume and GIA Volume

Next, we measured the absolute volumes of PAE for the entire patient cohort and separately for the 4 subgroups outlined above (MCA, posterior circulation, frontotemporal, and brainstem). Overall median PAE volume was 13.8 cm³ (95% CI 3.2–28.9; Fig. 4 upper). Perianeurysmal edema volume was significantly larger in GIAs of the MCA than those of the posterior circulation ($p < 0.01$). Furthermore, PAE of GIAs with frontotemporal mass effect was significantly larger than the PAE of GIAs with brainstem mass effect ($p < 0.01$).

FIG. 1. Bar graphs of the proportions of Gliomas without and with PAE for each parent vessel of the Glioma (left) and each location of mass effect caused by the Glioma (right). cav. = cavernous; supraclin. = supraclinoid; post. = posterior circulation.

We then examined whether the volume of PAE was related to the volume of the Glioma. For the entire patient cohort, we found a correlation between volumes of PAE and Glioma with an r_s of 0.51 ($p = 0.01$). This correlation was more pronounced in Gliomas of the MCA ($r_s = 0.69$, $p = 0.01$) and in Gliomas with frontotemporal mass effect ($r_s = 0.73$, $p = 0.02$). For Gliomas of the posterior circulation, there was no correlation between Glioma volume and PAE volume ($p = 0.44$).

To examine how the volumes of PAE and Glioma compared with each other, we calculated the relative PAE volume as the ratio of absolute PAE volume/Glioma volume (Fig. 4 lower). For the entire patient cohort, we found a relative PAE volume of 1.07 (95% CI 0.17–1.60), which indicates that PAE volumes were slightly larger than the Glioma volumes. In Gliomas of the MCA and in those with frontotemporal mass effect, this ratio was even larger; Gliomas of the posterior circulation and Gliomas with mass effect on

the brainstem both showed relative PAE volumes below 0.20, indicating that at these locations PAE volumes were smaller than Glioma volumes. Consequently, the difference in relative PAE volumes between Gliomas of the MCA and of the posterior circulation was significant ($p = 0.02$), as was the difference between relative PAE volumes of Gliomas with mass effect at a frontotemporal location and those with mass effect on the brainstem ($p = 0.04$).

Perineurysmal Edema and PT

Partial thrombosis was present in 68.1% of the entire patient cohort and was observed at all Glioma locations. It was most common in Gliomas of the MCA (94.4%), followed by Gliomas of the ACA (83.3%), the posterior circulation (80.0%), the cavernous ICA (43.5%), and the supraclinoid ICA (42.9%). Interestingly, 95.7% of Gliomas with PAE displayed PT compared with 54.3% of Gliomas without PAE.

Clinical Presentation

Clinical data from the time of MRI diagnosis were available for 66 of 69 cases. There was no difference between patients without PAE and those with PAE as regards the occurrence of hemiparesis ($p = 0.82$) or aphasia ($p = 0.61$). For the entire patient cohort, the mRS score ranged between 0 and 4, with no symptoms (mRS 0) in 19.0% of the patients without PAE and in 33.3% of the patients with PAE. Respectively, 52.4% and 42.9% of patients had an mRS Score 1; 16.7% and 14.3%, Score 2; 9.5% and 9.5%, Score 3; and 2.4% and 0%, Score 4. When comparing the mRS scores of both groups, we found that the presence of PAE had no influence on patient clinical presentation ($p = 0.30$).

Discussion

The prevalence and potential causes of PAE in intracranial aneurysms have not been systematically examined. In this multicenter study, 69 Gliomas were analyzed and PAE was observed in 33.3% of all cases. The Glioma volume and the presence of PT were significant risk factors for PAE formation.

FIG. 2. Bar graph of the location of Glioma mass effect and corresponding Glioma parent vessels.

FIG. 3. Box plot of the volumes of GIAs with (+) and without (-) PAE. *p < 0.05.

Perianeurysmal Edema and GIA Location

Even though GIA location was not a risk factor for PAE formation, we found that PAE predominantly occurred in GIAs of the MCA with mainly frontotemporal mass effect and in GIAs of the posterior circulation with mass effect on the brainstem. It is remarkable that GIAs located at the cavernous ICA did not cause any PAE even though they exerted mass effect on the brain (Figs. 1 and 2). It seems reasonable to speculate that this unique finding could be explained by the dura mater acting as a protective barrier between the GIA surface and brain parenchyma at this specific location, which is not the case in GIAs at other locations. This theory is supported by the results of 2 case series in patients with partially thrombosed large intracranial aneurysms and GIAs.^{9,11} These series are comparable in terms of the number of patients (21 vs 23) and the mean aneurysm diameter (27.0 vs 29.9 mm). Remarkably, they mainly differ in the proportion of extradural aneurysms (9.5% vs 34.8%) and in the frequency of PAE (81% vs 14%).

Perianeurysmal Edema and GIA Volume

In our patient cohort GIA volume was a significant risk factor—not only for the occurrence of PAE but also for PAE volume. This relation was not observed in GIAs of the posterior circulation.

The mass effect resulting from increasing volumes of intracranial aneurysms has been described to reduce the perfusion of surrounding brain parenchyma and thereby cause PAE.^{6,10} Our results are in accordance with these assumptions since GIAs with PAE were significantly larger than those without PAE. Another important aspect of aneurysmal mass effect is the potential compression of the venous system. In stroke and venous malformations, perilesional edema has been shown to occur after cerebral veins are occluded or thrombosed.¹⁵ In our study, the highest proportion of GIAs with PAE was observed in GIAs of the MCA with simultaneous mass effect on both the

FIG. 4. Box plot of absolute (upper) and relative (lower) volumes of PAE in relation to the GIA parent vessel and the location of GIA mass effect. *p < 0.05.

frontal and the temporal lobes. Giant intracranial aneurysms at this specific location extend into the sylvian fissure, which contains important veins draining blood from temporal and frontal lobes. One might speculate that the relatively high frequency of PAE at this site could partially be caused by direct compression of these veins or their branches. In contrast, GIAs of the ICA within the cavernous sinus showed no PAE at all. At this particular location, complete compression of a large venous vessel, such as the cavernous sinus, seems less likely to occur. Nevertheless, since PAE has been described in smaller aneurysms as well, the theory of mass effect may only offer a partial explanation for the evolution of PAE.⁷

Perianeurysmal Edema and PT

Our data indicate that, in addition to GIA volume, the presence of PT may be a significant risk factor for the occurrence of PAE: PT was observed in almost all GIAs with PAE and in only about half of the GIAs without PAE. An association of PAE with PT of large intracranial aneurysms and GIAs has already been suspected, but our study is the first to systematically describe a potential causal relationship.^{5,6} Recently, inflammatory processes within the aneurysm wall, such as leukocyte invasion and

degradation of cellular matrix proteins, were shown to maintain a balance between aneurysm wall degeneration and repair.^{4,16} During such complex remodeling processes, repetitive bleedings and thromboses can occur, which is why PT in GIAs has been described as located not only within the aneurysm lumen but also within the aneurysm wall.^{1,13} A causal relationship between intracerebral thrombus and edema is known from ICH, in which the formation of perihematomal edema is largely attributed to thrombin and degradation products of hemoglobin, which are secreted by thrombosed parts of the ICH into surrounding brain parenchyma.¹⁸ Although this concept may not be completely transferable to GIA, metabolic factors secreted from thrombosed parts of the GIA wall may diffuse into neighboring brain parenchyma and subsequently induce PAE. The fact that we found no PAE in GIAs of the cavernous ICA leads us to speculate that the dura mater may protect the brain parenchyma from direct contact with the partially thrombosed surface of the GIA. This protective layer may effectively prevent the diffusion of PAE-inducing factors from the GIA wall into the neighboring brain parenchyma. So even though in our patient cohort GIAs of the cavernous sinus ICA did exert mass effect on the brain (Fig. 2) and did display PT, their extradural location seemed to shield the brain from PAE.

Clinical Implications

In contrast to the general assumption that PAE may aggravate the patient's clinical condition, our results showed no difference in neurological deficits between patients with and those without PAE. An explanation for this may be that the majority of neurological deficits are most likely caused by the direct mass effect exerted by the GIA itself rather than by subsequent PAE. Furthermore, our cohort largely consisted of patients at the initial diagnosis. Even though clinical trial evidence on the natural history of PAE is lacking, one may speculate that PAE plays a more pronounced clinical role at later time points during the course of the disease as well as in posttreatment morbidity. Nevertheless, as PAE represents a pathological alteration of brain parenchyma, changes in PAE may serve as a radiological marker of treatment success over time. Further investigation of long-term imaging follow-up data on GIA and PAE is required to test this hypothesis.

Study Limitations

The strength of our study lies in the fact that it is the first to systematically examine the phenomenon of PAE in untreated intracranial aneurysms. However, certain limitations exist. For one, the number of cases (69) included in the study may be viewed as rather limited. Nevertheless, GIAs are very rare lesions, and therefore case numbers in clinical studies on GIA are not directly comparable to expected case numbers in studies on smaller intracranial aneurysms. After all, a multicenter approach was necessary to reach the number of cases presented here. Another limitation is that we were only able to include those cases from the GIA registry for which MRI data were available in the registry's imaging database. This nonconsecutive inclusion into this specific study may serve as a potential bias. Moreover, MRI slice thickness was rather inhomoge-

neous since there were no strict rules on MRI modalities because of the nonstandardized nature of the GIA registry imaging library. Furthermore, for some GIA locations, especially the ACA (6 cases) or the supraclinoid ICA (7 cases), the number of cases was not large enough to allow for more detailed analyses.

Conclusions

In our patient cohort the occurrence of PAE depended on GIA volume and the presence of PT. Out of all GIA locations examined, PAE was observed most frequently in GIAs of the MCA, which is also where the largest volumes of both GIAs and PAE were found. As GIAs of the cavernous ICA were not associated with PAE, even though they exerted mass effect on the brain and despite the presence of PT, their separation from the brain parenchyma by the dura mater may prevent the diffusion of edema-inducing factors. Therefore, direct contact between the partially thrombosed surface of the GIA and the brain parenchyma may be crucial for PAE formation. As PAE remained a subclinical phenomenon in our patient cohort, which mainly consisted of patients at the initial diagnosis, further long-term evaluation is warranted.

Appendix

Giant Intracranial Aneurysm Study Group Members

Vajkoczy P, Maldaner N, Uebelacker A, Dengler J, Department of Neurosurgery, Charité–Universitätsmedizin Berlin, Germany; Endres M, Department of Neurology, Charité–Universitätsmedizin Berlin, Germany; Bohner G, Wiener E, Bauknecht HC, Department of Neuroradiology, Charité–Universitätsmedizin Berlin, Germany; Heuschmann PU, Malzahn U, Institute of Clinical Epidemiology and Biometry, University of Würzburg, Germany; Gläsker S, Zentner J, Van Velthoven V, Department of Neurosurgery, University Hospital Freiburg, Germany; Guhl S, Schroeder HWS, Department of Neurosurgery, University of Greifswald, Germany; Strowitzki M, Department of Neurosurgery, Trauma Center Murnau, Germany; Etminan N, Haegggh D, Eicker S, Turowski B, Department of Neurosurgery, University of Düsseldorf, Germany; Schebesch KM, Brawanski A, Department of Neurosurgery, University of Regensburg, Germany; Wrede K, Sure U, Department of Neurosurgery, University of Essen, Germany; Schmidt NO, Regelsberger J, Westphal M, Department of Neurosurgery, University Medical Center, Hamburg Eppendorf, Germany; Mielke D, Rohde V, Department of Neurosurgery, Georg-August-University Göttingen, Germany; Hosch H, Moskopp D, Department of Neurosurgery Vivantes-Klinikum im Friedrichshain, Berlin, Germany; Joedicke A, Department of Neurosurgery Vivantes-Klinikum Neukoelln, Berlin, Germany; Hohaus C, Meisel HJ, Department of Neurosurgery, BG-Clinic Bergmannstrasse, Halle, Germany; Wostrack M, Meyer B, Lehmeberg J, Department of Neurosurgery, Technical University of Munich, Germany; Musahl C, Hopf N, Department of Neurosurgery, Klinikum Stuttgart, Germany; Winkler G, Spetzger U, Department of Neurosurgery, Klinikum Karlsruhe, Germany; Graewe A, Meier U, Department of Neurosurgery, Unfallkrankenhaus Berlin, Germany; Hong B, Nakamura M, Krauss J, Department of Neurosurgery, Hannover Medical School, Hannover, Germany; Grote A, Simon M, Schramm J, Department of Neurosurgery, University Hospital Bonn, Germany; Kursumovic A, Rath SA, Department of Neurosurgery and Interventional Neuroradiology, Donau-Isar-Klinikum, Deggendorf, Germany; Marbacher S, Fathi A, Fandino J, Department of Neurosurgery, Kantonsspital Aarau, Switzerland; Familiari P, Raco A, Department of Neurosurgery, University of Rome “Sapienza,” Rome, Italy; Bijlenga

P, Schaller K, Service de Neurochirurgie, Faculté de Médecine de Genève and Hôpitaux Universitaire de Genève, Switzerland; Gruber A, Wang WT, Knosp E, Department of Neurosurgery, Medical University Vienna, Austria; Hoffmann KT, Boxhammer E, Department of Neuroradiology, University of Leipzig, Germany; Rüfenacht DA, Department of Neuroradiology, Klinik Hirslanden, Zurich, Switzerland; Boccardi E, Piano M, Department of Neuro-radiology, Ospedale Niguarda Ca' Granda, Milan, Italy; Niemelä M, Nurminen V, Lehecka M, Hernesniemi J, Department of Neurosurgery, Helsinki University Central Hospital, Helsinki, Finland; Burkhardt JK, Bozinov O, Regli L, Department of Neurosurgery, University Hospital of Zurich, Switzerland; Shekhtman OD, Eliava SS, Burdenko Neurosurgical Institute, Russian Academy of Medical Sciences, Moscow, Russia; Kato N, Irie K, Nishimura K, Kaku S, Arakawa H, Yuki I, Ishibashi T, Murayama Y, Department of Neurosurgery, Jikei University School of Medicine, Tokyo, Japan; Fiss I, Kombos T, Department of Spine Surgery and Neurosurgery, Helios Klinikum Hildesheim, Germany; Pedro MT, König R, Wirtz R, Department of Neurosurgery, University Hospital of Ulm, Germany; Helthuis J, van der Zwan A, Department of Neurosurgery, University Medical Center Utrecht, Netherlands; Cognard C, Gawlitza M, Department of Neuroradiology, Toulouse University Hospital, Toulouse, France; Wanke I, Institute of Diagnostic and Interventional Radiology and Neuroradiology, University of Essen, Germany; Fiedler J, Department of Neurosurgery, Budweis Hospital, Czech Republic.

References

- Alvarez H: Etiology of giant aneurysms and their treatment. **AJNR Am J Neuroradiol** 30:E8–E10, 2009 (Letter)
- Carrillo JA, Lai A, Nghiemphu PL, Kim HJ, Phillips HS, Kharbanda S, et al: Relationship between tumor enhancement, edema, IDH1 mutational status, MGMT promoter methylation, and survival in glioblastoma. **AJNR Am J Neuroradiol** 33:1349–1355, 2012
- Dengler J, Heuschmann PU, Endres M, Meyer B, Rohde V, Rüfenacht DA, et al: The rationale and design of the Giant Intracranial Aneurysm Registry: a retrospective and prospective study. **Int J Stroke** 6:266–270, 2011
- Frösen J, Piippo A, Paetau A, Kangasniemi M, Niemelä M, Hernesniemi J, et al: Remodeling of saccular cerebral artery aneurysm wall is associated with rupture: histological analysis of 24 unruptured and 42 ruptured cases. **Stroke** 35:2287–2293, 2004
- Halbach VV, Higashida RT, Dowd CF, Barnwell SL, Fraser KW, Smith TP, et al: The efficacy of endosaccular aneurysm occlusion in alleviating neurological deficits produced by mass effect. **J Neurosurg** 80:659–666, 1994
- Heros RC, Kolluri S: Giant intracranial aneurysms presenting with massive cerebral edema. **Neurosurgery** 15:572–577, 1984
- Hui T, Tsutsumi K, Kitagawa N, Hayashi K, Ujifuku K, Yasunaga A, et al: Progressive perianeurysmal edema preceding the rupture of a small basilar artery aneurysm. **Clin Neurol Neurosurg** 111:216–219, 2009
- Kondoh T, Fujita K, Yamashita H, Shirakata M, Tamaki N, Matsumoto S: Giant intracranial aneurysms—magnetic resonance imaging follow-up and clinical symptoms. **Neurol Med Chir (Tokyo)** 31:330–335, 1991
- Krings T, Alvarez H, Reinacher P, Ozanne A, Baccin CE, Gandolfo C, et al: Growth and rupture mechanism of partially thrombosed aneurysms. **Interv Neuroradiol** 13:117–126, 2007
- Nakayama Y, Tanaka A, Ohshiro S, Yoshinaga S: Extensive edema in the thalamus caused by thrombosed basilar artery aneurysm. **Neurol Med Chir (Tokyo)** 38:274–277, 1998
- Roccatagliata L, Guédin P, Condette-Auliac S, Gaillard S, Colas F, Boulain A, et al: Partially thrombosed intracranial aneurysms: symptoms, evolution, and therapeutic management. **Acta Neurochir (Wien)** 152:2133–2142, 2010
- Schoenegger K, Oberndorfer S, Wuschitz B, Struhal W, Hainfellner J, Prayer D, et al: Peritumoral edema on MRI at initial diagnosis: an independent prognostic factor for glioblastoma? **Eur J Neurol** 16:874–878, 2009
- Schubiger O, Valavanis A, Wichmann W: Growth-mechanism of giant intracranial aneurysms; demonstration by CT and MR imaging. **Neuroradiology** 29:266–271, 1987
- Simard JM, Kent TA, Chen M, Tarasov KV, Gerzanich V: Brain oedema in focal ischaemia: molecular pathophysiology and theoretical implications. **Lancet Neurol** 6:258–268, 2007
- Stam J: Thrombosis of the cerebral veins and sinuses. **N Engl J Med** 352:1791–1798, 2005
- Tulamo R, Frösen J, Hernesniemi J, Niemelä M: Inflammatory changes in the aneurysm wall: a review. **J Neurointerv Surg** 2:120–130, 2010
- Wiebers DO, Whisnant JP, Huston J III, Meissner I, Brown RD Jr, Piegras DG, et al: Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. **Lancet** 362:103–110, 2003
- Xi G, Hua Y, Keep RF, Younger JG, Hoff JT: Systemic complement depletion diminishes perihematomal brain edema in rats. **Stroke** 32:162–167, 2001

Author Contributions

Conception and design: Dengler, Schmidt. Acquisition of data: Dengler, Maldaner, Bijlenga, Burkhardt, Graewe, Guhl, Hong, Hohaus, Kursumovic, Mielke, Schebesch, Wostrack, Vajkoczy, Schmidt. Analysis and interpretation of data: Dengler, Schmidt. Drafting the article: Dengler, Vajkoczy, Schmidt. 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: Dengler. Statistical analysis: Dengler. Administrative/technical/material support: Rüfenacht, Vajkoczy. Study supervision: Dengler, Schmidt.

Correspondence

Julius Dengler, Department of Neurosurgery, Charité, Campus Virchow Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany. email: julius.dengler@charite.de.