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ORIGINAL ARTICLE - VASCULAR NEUROSURGERY - ANEURYSM

Clinical implications and radiographic characteristics of the relation between giant intracranial aneurysms of the posterior circulation and the brainstem

Julien Haemmerli[1,2] · Pavlina Lenga[1] · Bujung Hong[3] · Adisa Kursumovic[4] · Nicolai Maldaner[5] · Jan-Karl Burkhardt[5] · Philippe Bijlenga[2] · Daniel A. Rüfenacht[6] · Nils-Ole Schmidt[7] · Peter Vajkoczy[1] · Julius Dengler[1,8,9]

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Abstract

Background Giant intracranial aneurysms of the posterior circulation (GPCirA) are rare entities compressing the brainstem and adjacent structures. Previous evidence has shown that the amount of brainstem shift away from the cranial base is not associated with neurological deficits. This raises the question whether other factors may be associated with neurological deficits.

Methods All data were extracted from the Giant Intracranial Aneurysm Registry, an international multicenter prospective study on giant intracranial aneurysms. We grouped GPCirA according to the mass effect on the brainstem (lateral versus medial). Brainstem compression was evaluated with two indices: (a) brainstem compression ratio (BCR) or diameter of the compressed brainstem to the assumed normal diameter of the brainstem and (b) aneurysm to brainstem ratio (ABR) or diameter of the aneurysm to the diameter of the compressed brainstem. We examined associations between neurological deficits and GPCirA characteristics using binary regression analysis.

Results Twenty-eight GPCirA were included. Twenty GPCirA showed medial (71.4%) and 8 lateral compression of the brainstem (28.6%). Baseline characteristics did not differ between the groups for patient age, aneurysm diameter, aneurysm volume, modified Rankin Scale (mRS), motor deficit (MD), or cranial nerve deficits (CND). Mean BCR was 53.0 in the medial and 54.0 in the lateral group ($p = 0.92$). The mean ABR was 2.9 in the medial and 2.3 in the lateral group ($p = 0.96$).

In the entire cohort, neither BCR nor ABR nor GPCirA volumes were associated with the occurrence of CND or MD. In contrast, disability (mRS) was significantly associated with ABR (OR 1.94 (95% CI 1.01–3.70; $p = 0.045$) and GPCirA volumes (OR 1.21 (95% CI 1.01–1.44); $p = 0.035$), but not with BCR.

Conclusion In this cohort of patients with GPCirA, neither the degree of lateral projection nor the amount of brainstem compression predicted neurological deficits. Disability was associated only with aneurysm volume. When designing treatment

This research was carried out at the Department of Neurosurgery, Charité-Universitaetsmedizin Berlin, Germany.

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✉ Julien Haemmerli
Julien.haemmerli@hcuge.ch

[1] Department of Neurosurgery, Charité-Universitaetsmedizin Berlin, Berlin, Germany

[2] Department of Neurosurgery, University Hospital Geneva, Geneva, Switzerland

[3] Department of Neurosurgery, Hannover Medical School, Hanover, Germany

[4] Department of Neurosurgery and Interventional Neuroradiology, Donauisar Klinikum Deggendorf, Deggendorf, Germany

[5] Department of Neurosurgery, University Hospital of Zurich, Zurich, Switzerland

[6] Department of Neuroradiology, Hirslanden Clinic, Zurich, Switzerland

[7] Department of Neurosurgery, University Medical Center, Eppendorf, Hamburg, Germany

[8] Brandenburg Medical School Theodor Fontane, Campus Bad Saarow, Bad Saarow, Germany

[9] Department of Neurosurgery, Helios Clinic, Bad Saarow, Germany

strategies for GPCirA, aneurysm laterality or the amount of brainstem compression should be viewed as less relevant while the high risk of rupture of such giant lesions should be emphasized.
Trial registration The registry is listed at clinicaltrials.gov under the registration no. NCT02066493.

Keywords Giant intracranial aneurysms · Unruptured · Posterior fossa

Introduction

Giant intracranial aneurysms are rare entities defined by a diameter of at least 25 mm and account for 5% of all intracranial aneurysms [1–8]. Giant intracranial aneurysms of the posterior circulation (GPCirA) are even more infrequent and associated with high morbidity and mortality, even when treated [2–5, 8–11]. They arise from the vertebral, basilar, or cerebellar arteries. Because of the small size of the posterior fossa, unruptured GPCirA exert substantial mass effect on the brainstem and the adjacent cranial nerves, leading to cranial nerve palsy, motor impairment, hydrocephalus, or various levels of disability [2–5, 9, 10, 12]. Potential consequences of the mass effect on the brainstem were reported in previous case reports [4, 6, 12–14].

As far as we know, no study has focused on the relation between the localization of the GPCirA and the degree of disability, as well as the relation between the compression of the brainstem and neurological deficits. Lenga et al. showed that only the size of the GPCirA was associated with neurological deficits while brainstem displacement from the cranial base had no influence on the occurrence of neurological deficits [4].

Because GPCirA are slow-growing lesions, they may be compared with foramen magnum meningiomas with regard to their clinical presentation. Bruneau et al. proposed a classification of meningiomas of the foramen magnum based on their position around the brainstem (lateral versus medial) [15].

This work is aimed at analyzing the relation between the laterality of the GPCirA and the clinical presentation and the degree of brainstem compression and its relevance for neurological deficits.

Methods

Giant Aneurysm Registry imaging database

All data were collected from the database of the Giant Intracranial Aneurysm Registry, an international multicenter prospective observational study exclusively focusing on giant intracranial aneurysms. The ethics committee of the Charité Berlin (EA2/052/08) and of each participating center approved data collection. Each participating subject or their relatives gave written consent. The registry is listed at clinicaltrials.gov under the registration no. NCT02066493. Patients were included into this specific study if they were diagnosed with a GPCirA.

Imaging analysis

All imaging data were analyzed using the software "iPlan Cranial" (BrainLab, Heimstetten, Germany). MRI with time-of-fight (TOF) sequences, MRI with T2-weighted sequences, and CT angiograms were used to analyze the position of the GPCirA and its interaction with regard to the brainstem.

Figure 1 describes the classification of the laterality of the brainstem compression. On the axial images that contained the largest GPCirA diameter, two lines were drawn that originated from the pontocerebellar angle and reached the lateral extremities of the clivus. The space between the two lateral lines was defined as "*medial*." The space lateral to the lateral lines was defined as "*lateral*." If the aneurysm was placed between the medial and the lateral space, it was also defined as "*medial*." Figure 2 gives an example of a lateral GPCirA (a) and a medial GPCirA (b).

To describe the compression of the brainstem, two indices were established: (1) the *brainstem compression ratio* (BCR) (Fig. 3), which relates the diameter of the compressed brainstem to the assumed normal diameter of the brainstem without any compression and (2) the *aneurysm to brainstem ratio* (ABR) (Fig. 4), which relates

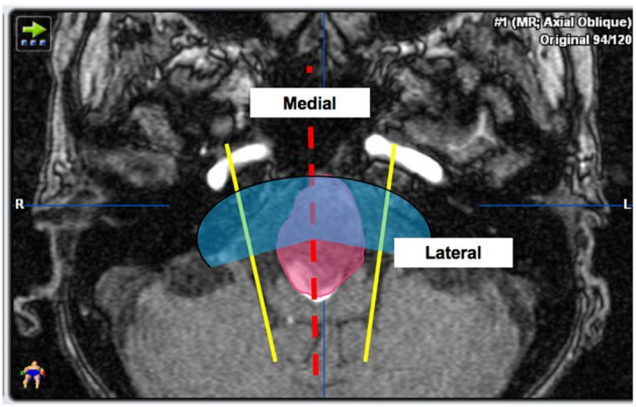

Fig. 1 Definition of the position of the aneurysm, lateral versus medial

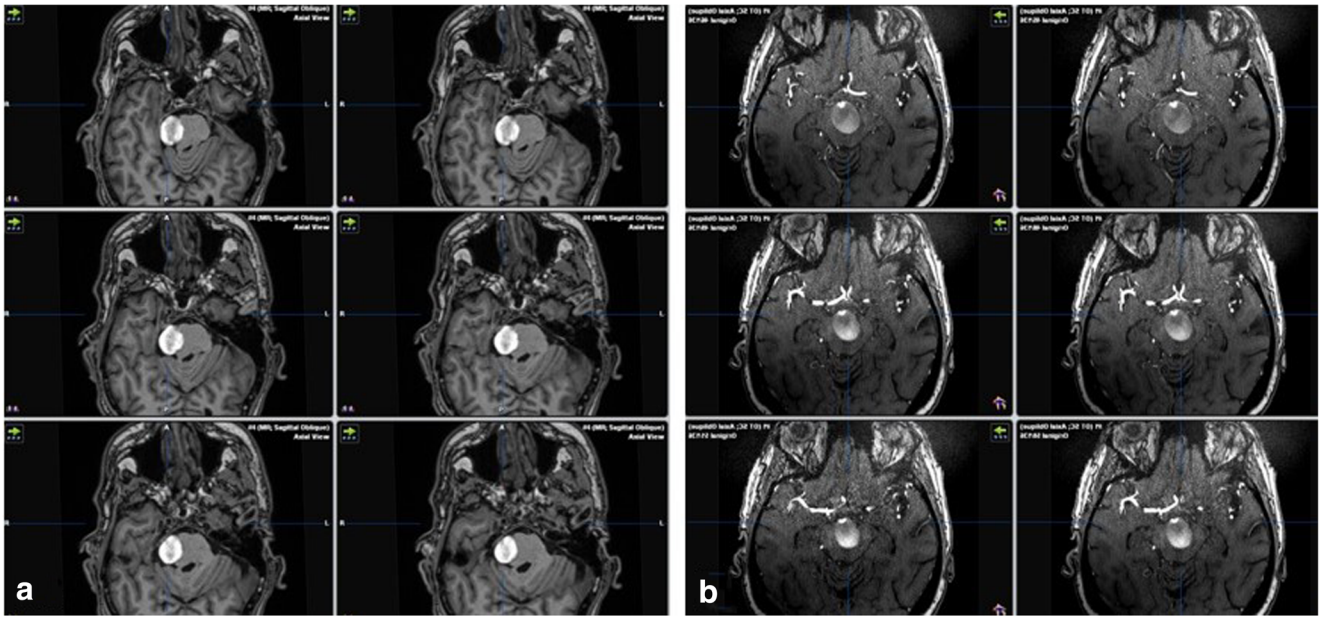

Fig. 2 Examples of lateral and medial aneurysms. **a** Lateral GPCirA. **b** Medial GPCirA

the diameter of the aneurysm to the diameter of the compressed brainstem. Both values were acquired on an axial slice of MRI, in which the maximum GPCirA diameter was observed.

The aneurysm volume and diameter had been previously measured by two authors (J.D; P.L). All other measurements were performed by the first author (J.H).

Clinical data

Clinical data such as sex, age, motor deficit, cranial nerve deficit, and modified Rankin Scale (mRS) score were analyzed. According to the analysis from Weisscher et al. for patients after stroke [16], mRS was defined as *low level of disability* for a score between 0 and 2. A *high level of disability* was defined as a score between 3 and 6. MD and CND were defined as "*present*" or "*absent*." There were no missing data. All data were documented prior to any surgical or endovascular treatment.

Statistical analysis

Statistical analysis was performed using the software SPSS, version 24.0.0.0 (IBM Corp., Armonk, NY, USA). For all clinical and imaging data, a Shapiro-Wilk test was used to examine the normal distribution of the variables. A *t* test was performed for all normally distributed continuous variables (age, volume). A Mann-Whitney *U* test was done for the not parametric variable aneurysm diameter. Categorical variables were tested with a chi-square analysis. To measure the association between the categories lateral versus medial and the other characteristics, a binary regression analysis was performed. A separate regression model was used to examine the rela-

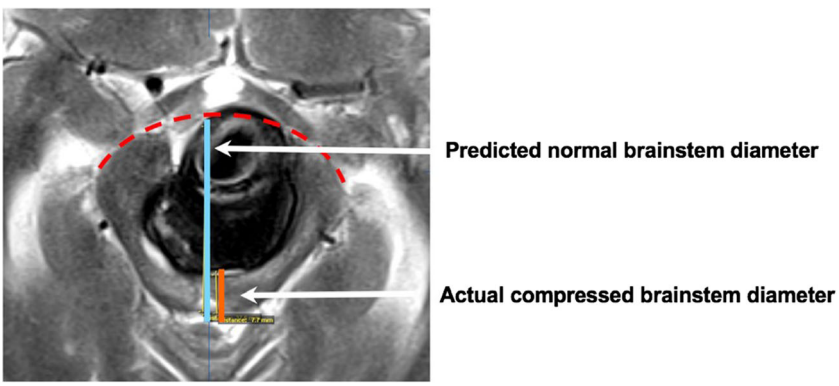

Fig. 3 *Brainstem compression ratio* (BCR), or the ratio between the diameter of the compressed brainstem and the assumed normal diameter of the brainstem without any compression

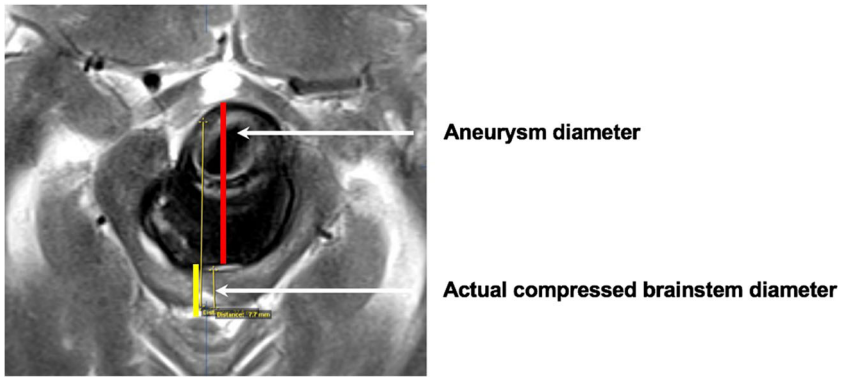

Fig. 4 *Aneurysm to brainstem ratio* (ABR), ratio between the diameter of the aneurysm and the diameter of the compressed brainstem

tion between the ABR and BCR and the neurological deficit/mRS. A p value < 0.05 was defined as representing statistically significant differences.

Results

Twenty-eight patients with an unruptured GPCirA, all of which had been included into the GIA (Giant Intracranial Aneurysm) Registry between January 2009 and March 2017, were enrolled in this study.

GPCirA laterality and GPCirA characteristics

Baseline characteristics for patients and GPCirA are presented in Table 1. No significant statistical difference was found between the two groups (lateral versus medial brainstem compression).

As shown in Table 2, we found no association between the location of the GPCirA and the previous variables (CND cranial nerve deficit $p = 0.53$; MD motor deficit $p = 0.24$).

Table 1 Patient and aneurysmal characteristics

	Lateral	Medial	p value
No. of patients (%)	8 (28.6)	20 (71.4)	
Age (SD)	65.6 (12.2)	58.5 (13.2)	0.20
Female, no. (%)	0 (0.0)	4 (20.0)	0.17
Cranial nerve deficit, no. (%)	3 (37.5)	12 (60.0)	0.28
Motor deficit, no. (%)	1 (12.5)	9 (45.0)	0.10
mRS, mean (SD)	1.5 (1.2)	2.1 (1.2)	0.67
Aneurysmal volume (cm^3) (SD)	9.4 (6.0)	10.1 (7.3)	0.80
Aneurysmal diameter (mm) (SD)	33.2 (6.3)	36.4 (8.0)	0.31
Brainstem compression ratio (SD)	54.0 (9.3)	53.0 (4.8)	0.93
Aneurysm to brainstem ratio (SD)	2.3 (0.56)	2.9 (0.68)	0.96

Associations between BCR/ACR and neurological deficits

In subjects with CND (cranial nerve deficit) (15 patients, 53.6%), the mean BCR was 50.0 (SD ± 23.2) and the mean ABR 1.9 (SD ± 1.4). Both ratios did not differ significantly from those measured in patients without CND, where we observed a BCR by 57.1 (SD ± 21.6) ($p = 0.41$) and an ABR by 3.6 (SD ± 3.6) ($p = 0.12$).

In patients with MD motor deficit ($n = 10$, 36.7%), the BCR was 52.9 (SD ± 24.9) and ABR 3.0 (SD ± 4.1) and did not differ from the ratios measured in subjects without MD motor deficit.

When comparing subjects with low disability (mRS 0–2) to those with high disability (mRS 3–6), a significant difference was found for the ABR (1.9 (SD ± 1.2) versus 4.7 (SD ± 4.3); $p = 0.03$). BCR did not differ between both disability groups ($p = 0.11$).

We also found GPCirA volumes to differ according to disability. Subjects with low disability showed volumes of 7.9 cm^3 (SD ± 4.7) versus 15.1 cm^3 (SD ± 8.9; $p = 0.02$) in subjects with high disability.

Associations between ABR and disability and ABR and GPCirA volumes are displayed in Tables 3 and 4.

Table 2 Binary regression analysis. Independent factors: age, CND, MD, mRS, and volume. Dependent factors: *lateral* versus *medial* brainstem compression

	Regression coef.	Standard error	OR (95% CI)	p value
Cranial nerve deficit	− 0.601	0.960	0.548 (0.08–3.6)	0.53
Motor deficit	− 1.437	1.216	0.238 (0.02–2.58)	0.24
mRS	− 0.217	0.479	0.805 (0.32–2.06)	0.65
Aneurysmal volume	− 0.004	0.091	0.996 (0.81–1.2)	0.96

Table 3 BCR, ABR, and aneurysm volume according to the presence or not of CND and MD and according to the level of disability. Boldface type indicates statistical significance

	mRS groups			CND groups			MD groups		
	Low disability	High disability	*p* value	CND	no CND	*p* value	MD	no MD	*p* value
BSR, mean	49.0	64.1	0.11	50.0	57.1	0.41	52.9	53.5	0.94
ABR, mean	1.9	4.7	**0.03**	1.9	3.6	0.12	3.0	2.5	0.68
Volume, mean	7.9	15.1	**0.02**	8.1	12.0	0.21	10.4	9.8	0.96

Discussion

The main result of our study on patients with GPCirA is that neurological deficits or disability were associated neither with the laterality nor with the degree of brainstem compression itself. Disability was predicted only by the relation between GPCirA size and the size of the compressed brainstem. Interestingly, the occurrence of CND or MD was not associated with any of the examined radiographic variables. Only the volume of GPCirA was associated with poor outcome (mRS 4–6).

Surgical and endovascular treatment strategies for GPCirA are predominantly based on the exact aneurysm location, its relation to the brainstem, as well as on the amount of neurological deficits. Decision-making algorithms on treatment and surgical approaches resemble those in posterior fossa meningiomas. Recently, Bruneau et al. proposed a classification of foramen magnum meningiomas based on their position on preoperative MRI [15]. Although this classification was primarily meant to differentiate surgical approaches and not related to clinical symptoms, we transferred the main principles of their classification to our study, classifying the GPCirA as "lateral" or "medial.". Peraio et al. conducted a retrospective study on 174 posterior fossa meningiomas with invasion of the internal auditory canal and brainstem compression. In this study, a preoperative assessment of the participating subjects as well as the postoperative complications was conducted [17]: dysphagia, facial numbness, diplopia, or trigeminal neuralgia were found to be caused by the mass effect of the meningioma. However, the position of the meningioma and its extent were not analyzed. These two studies are aimed at understanding and characterizing the relation between posterior fossa meningiomas and neurological deficits. In the same way, our study is aimed at highlighting the relation of radiographic characteristics of GPCirA and the brainstem. As far as we know, the association between the position of GPCirA and neurological status represents a novelty in the literature.

Table 4 Regression analysis for ABR and volume. Dependent factors: low versus high disability; independent factors: ABR and volume. Boldface type indicates statistical significance

	Regression coef	SE	Wald	Odds ratio (95% CI)	*p* value
ABR	0.66	0.33	4.03	1.94 (1.01–3.70)	**0.045**
Volume	0.19	0.09	4.46	1.21 (1.01–1.44)	**0.035**

In a previous study from the GIA Registry group, laterality was an important risk factor for neurological deficits in GIA of the cavernous carotid artery [4]. This association was explained by the obvious concentration of cranial nerves at the lateral wall of the cavernous sinus, making this area more vulnerable to mass effects caused by GIA. We therefore hypothesized that the concept of laterality as a risk factor may be transferable to GIA of the posterior fossa. To explain why we were not able to establish such a relationship in GPCirA, one may point to certain anatomical differences when compared with the cavernous sinus. First of all, the cranial nerves 3–5 are fixed within the lateral wall of the cavernous sinus, while, in contrast, cranial nerves emanating from the brainstem run free between the brainstem and the cranial base foramina through which they exit. Therefore, the posterior cranial nerves may be able to dodge mass effects to a certain degree. Also, the consequence of medial mass effect on the brainstem (i.e., lesions to the cranial nerve nuclei within the brainstem) versus that of lateral mass effect (i.e., lesions to the cranial nerves more peripherally after exiting out of the brainstem) may, in the end, be the same. It may simply make no difference whether the nuclei are compromised, or the lesion affects the nerves more peripherally.

Another interesting result concerns the BCR and ABR. As a reminder, BCR represents the compression rate of the brainstem, not accounting for GPCirA characteristics, whereas ABR represents the compression of the brainstem in relation to aneurysm size. ABR can be viewed as a measure of the bulging of the aneurysm into the brainstem: a high ABR represents significant bulging into the brainstem (Fig. 5). Lenga et al. did not measure brainstem compression or bulging into the brainstem, yet

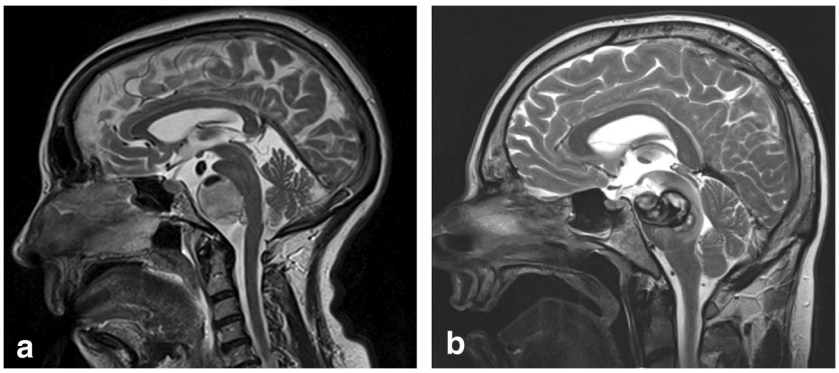

Fig. 5 GPCirA with a low ABR (**a**) and GPCirA with high ABR (**b**), representing the bulging into the brainstem

they showed that brainstem displacement had no influence on the appearance of neurological deficit in GPCirA and was not associated with high mRS score [5]. As we found that the compression rate of the brainstem (BCR) seems to have no relation with the occurrence of neurological deficit or disability in our study, one may argue that the brainstem has a capacity to adapt to slowly progressive stress.

Our study has some limitations. First of all, our analysis was conducted on 28 subjects with GPCirA. This case number is relatively low. However, giant aneurysms of the posterior fossa are rare entities, and our databank needed an international multicentric recruitment to achieve even this relatively low number. Also, our analysis was conducted retrospectively, and therefore, some selection bias may be present. In addition, our measurements were conducted only at the level of maximum brainstem compression and therefore do not account for compression effects at other levels of the brainstem. Finally, this study only examines baseline data before any type of treatment and does not evaluate any data on specific treatment types or outcomes thereof. Since clinical follow-up data of the registry will be published separately, our current results do not allow for suggestions on how to best treat GPCirA.

Conclusion

In patients with GPCirA, the degree of lateral projection or the amount of brainstem compression itself did not predict neurological deficits. Disability was associated only with aneurysm volume. When deciding on whether GPCirA should be treated or not, aneurysm laterality or the amount of brainstem compression should be viewed as less relevant while factors like the high risk of rupture of such giant lesions should be emphasized.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Charité-Universitaetsmedizin Berlin) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

Disclaimer The sponsor had no role in the design or conduct of this research.

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Comments The major risk of giant aneurysms in the posterior circulation is the risk of rupture (50% in 5 years, cumulative). Unless the patient is in a medical condition which makes a treatment contraindicated, I believe all basilar tip giant aneurysms should be given the same level of attention and be treated if a reasonable clinical setting is present. The fact that a laterally projecting aneurysm or a degree of compression is not impacting C/N or motor function is not a legit criteria to delay or not to treat an unruptured giant aneurysm. This is a well-designed study on a small population and lacks treatment data. I encourage the authors to provide us with their updated information on what treatment modality is used in this population and whether the projection and compressive factors of the aneurysm could/should impact the treatment modality.

Amir Dehdashti
NY, USA