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DISSERTATION

Analysis of potential risk factors for the occurrence of brainstem symptoms in subjects with giant intracranial aneurysms of the posterior circulation

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1 Abbreviations

GIA: giant intracranial aneurysm

IA: intracranial aneurysm

GPCirA= Giant posterior circulation aneurysm

McRL= McRae line

ΔMT = distance between McRae-line and highest tip of Giant posterior circulation aneurysm

PT= partial thrombosis

T2WI= T2-weighted image

mRS= modified Rankin Scale,

CND= cranial nerve deficit

MD= motor deficit

BI= basilar invagination

OR= odds ratio

r_s= Spearman correlation coefficient

IQR= interquartile range

SD=standard deviation

2 Summary

2.1 Abstract

Hintergrund

Intrakranielle Riesen-Aneurysmen im hinteren Stromkreis (GPCirA) rufen häufig einen erheblichen Masseneffekt auf den Hirnstamm hervor. Dadurch können neurologische Defizite verursacht werden. Es gibt keine systematische Analyse, um die Hauptgründe dieses Phänomens zu untersuchen. Hauptziel dieser Arbeit ist es, Risikofaktoren zu identifizieren, die verantwortlich für das Auftreten von Hirnnervenschädigung, motorischen Defiziten und die Behinderung von Patienten mit GPCirA sind.

Methodik

Präoperative MRTs von 30 unrupturierten GPCirA wurden retrospektiv analysiert. Die folgenden Faktoren wurden untersucht: das GPCirA Volumen, die GPCirA Durchmesser, das Vorkommen von Hydrozephalus, partielle Thrombosierung (PT), das PT Volumen und der Grad der Hirnstammverlagerung. Letzterer wurde als die Distanz zwischen der McRae Linie und der obersten Aneurysma-Spitze (∆MT) definiert. Wir haben mögliche Assoziationen zwischen den bereits genannten Faktoren und den neurologischen Defiziten untersucht.

Ergebnisse

Die Hälfte der Patienten hatten Hirnnervendefizite (n=15, 50.0%) und 33.3% motorische Defizite. Die Patienten mit Hirnnervenschädigung waren signifikant jünger (51y, SD 15.0 vs. 69.0y, SD 21.0; p=0.01) und hatten signifikant größere ∆MT als die Patienten ohne Hirnnervenschädigung (50.7mm, IQR 39.2-53.9 vs. 39.0mm, IQR 32.3-45.9; p=0.02). Die Patienten mit motorischem Defizit hatten größere ∆MT (50.5 mm, IQR 40.8-54.6 vs 39.1mm, IQR 32.8-50.5; p=0.04) im Vergleich zu den Fällen ohne motorisches Defizit. Patienten mit mRS 3-5 hatten größere GPCirA Volumina (14.9 cm^3, IQR 8.6-18.7) als die Patienten mit mRS 0-2 (6.8 cm^3, IQR 4.4-11.7; p=0.03). In der Regressionsanalyse zeigte sich, dass größere Aneurysma-Volumina mit einem höheren Behinderungsgrad assoziiert waren (OR=1.13; 95% CI 1.0-1.3; p=0.04), aber nicht mit der ∆MT. Keine der untersuchten Faktoren war mit dem Auftreten von der Hirnnervenschädigung oder motorischem Defizit assoziiert. Es zeigte sich auch keine Korrelation zwischen

Aneurysma-volumen und ΔMT. Letztlich gab es keine signifikanten Unterschiede zwischen den verschiedenen Lokalisationen der Aneurysmata im hinteren Stromgebiet in Bezug auf das Auftreten von neurologischen Defiziten.

Schlussfolgerungen

Aus den Ergebnissen dieser klinischen Studie lässt sich ableiten, dass nur das Volumen der GPCirA einen signifikanten Prädiktor für das Auftreten von neurologischen Defiziten darstellt, jedoch keiner der anderen untersuchten Risikofaktoren hatte einen signifikanten Einfluss auf den klinischen Zustand der Patienten. Diese Ergebnisse sind von klinischer Relevanz, da behandelnde Ärzte mit ihnen in der Lage sind, zusätzliche Argumente für und gegen eine Intervention bei GPCirA Patienten zu finden.

Object

Giant intracranial aneurysms of the posterior circulation (GPCirA) often cause compression of the brainstem and adjacent structures, resulting in neurological deficits. Using data from the Giant Intracranial Aneurysm (GIA) Registry, we designed a study to investigate potential predictors of cranial nerve deficits (CND), motor deficit (MD) and the modified Rankin Score (mRS) in subjects with GPCirA.

Methods

All data were extracted from the database of the GIA Registry, which is an international multicenter prospective observational study exclusively focusing on intracranial aneurysms with diameters of at least 25mm. In magnetic resonance imaging of 30 subjects with unruptured GPCirA we examined GPCirA volume and diameters, presence of hydrocephalus and partial thrombosis (PT), and the amount of displacement of the brainstem as measured by the distance between the McRae Line (McRL) and the tip of GPCirA (ΔMT). We also examined potential associations between these specific factors and neurological deficits

Results

Half of the patients presented with CND and 33.3% of the cases had MD. Patients with CND were different from those without CND in age (51y SD 15.0 vs. 69.0y SD 21.0; p=0.01) and in ΔMT (50.7mm, IQR 39.2-53.9 vs. 39.0mm, IQR 32.3-45.9; p=0.02). Patients with MD differed significantly from those without only in ΔMT (50.5 mm, IQR 40.8-54.6 vs 39.1mm, IQR 32.8-50.5; p=0.04). Patients with poor modified Rankin Score (mRS) had larger volumes (14.9 cm^3, IQR 8.6-18.7) compared to those with a good clinical condition (mRS 0-2) (6.8 cm^3, IQR 4.4-11.7; p=0.03). We found no differences between GPCirA locations (basilar apex, the basilar trunk, the vertebrobasilar junction and the vertebral artery) when we compared prevalences of neurological deficits. After performing multivariate regression analysis, adjusting for patient age, the occurrence of hydrocephalus and PT, higher degrees of disability were significantly associated with aneurysm volume (OR=1.13; 95% CI 1.0-1.3; p=0.04), but not with ΔMT. There were no associations between the presence of CND or MD and any of the examined variables.

Conclusions

Our data highlight that the GPCirA volume was the only predictor of patient neurological condition. None of the other examined factors, such like the brainstem displacements, the occurrence of hydrocephalus or PT or the location of GPCirA predicted the patient clinical condition. So, we feel that our results might suggest that, when we want to decide whether to treat or not GPCirA, we should always take into account firstly the volume of the aneurysms and we should examine in second line the other potential risk factors.

2.2 Introduction

Giant intracranial aneurysms (GIA) are rare entities, since they make up only about 2 to 5% of all intracranial aneurysms (IA) (24). Their uniqueness is reflected through their size, which starts at 25mm in diameter. GIA of the posterior circulation (GPCirA), defined as GIA originating from the vertebrobasilar arteries, are associated with the highest morbidity and mortality rates of all IA (7, 24). Different shapes, such as fusiform, dolichoectatic and transitional fusiform (9) and the occurrence of partial thrombosis (PT) are more commonly observed in GPCirA than in GIA of the anterior circulation (6). GPCirA frequently cause substantial compression of the structures located in the posterior fossa, such as the brainstem, the cerebellum and the adjacent cranial nerves (2, 26). Consequently, patients often present with neurological deficits, such as cranial nerve deficits (CND), motor deficits (MD), hydrocephalus, severe headaches or high degrees of disability (2, 12, 15,17). However, GPCirA have been investigated so far only as a byproduct of clinical studies examining predominantly smaller IA (14, 26). Accordingly, a systematical quantification of the degrees of brainstem compression caused by the giant mass effect and possible relations to clinical findings is still missing. In contrast, similar aspects have been investigated in detail in other pathologies of the cranial base, such as basilar invagination (BI). BI causes considerable compression of the brainstem since the odontoid tip protrudes into the posterior fossa putting significant stress on both brainstem and nuclei of cranial nerves (11, 19). In BI, brainstem displacement is quantified by the vertical distance between the odontoid tip and the so called “McRae line” (McRL), which connects the clivus and the opisthion. The pathological threshold was set to at least 5mm (4). Considering the anatomical relationships, the extension of the odontoid tip into the foramen magnum substantially compresses the brainstem and neighboring structures. Previous publications highlight that due to these compressive phenomena BI frequently leads to CND, MD, pulsatile headaches, neck pain and paresthesia (11, 19). While GPCirA are different entities from BI, many similarities do exist. GPCirA present with similar clinical symptoms and produce significant compression of the brainstem. Therefore, certain clinical and diagnostic tools established in the diagnosis of BI maybe transferrable to GPCirA. The distance between the McRL and the highest tip of the aneurysm (∆MT) may be used to estimate the degrees of brainstem displacement away from the cranial base and additionally might help to evaluate the patient’s clinical condition and their disability in actions of daily routine.

In previously published case series on GPCirA, the occurrence of clinical hydrocephalus is a common phenomenon, which is confirmed in computed tomography (CT) or magnetic resonance imaging (MRI) (12, 17). Their results suggest that the patients frequently experience significant disruption of the flow of the cerebrospinal fluid caused by the aneurysm's mass effect. However, nobody so far has systematically examined if the aneurysm mass effect is correlated to the occurrence of hydrocephalus or if the occurrence of hydrocephalus is the cause of the neurological deficits.

We designed a multicenter clinical study exclusively on unruptured GPCirA using clinical and imaging data from the database of the Giant Intracranial Aneurysm Registry with the aim to investigate the following points:

(1) Describe the clinical condition of subjects with GPCirA according to the occurrence of CND, MD, degrees of disability (modified Rankin scale, mRS), and hydrocephalus
(2) Describe GPCirA morphological parameters, such as diameter, volume and presence of PT as measured in MRI
(3) Examine the occurrence of hydrocephalus by using the Evans index (EI)
(4) Identify potential associations between GPCirA characteristics and clinical findings (CND, MD, mRS, hydrocephalus)
(5) Describe differences in prevalences of neurological deficits in relation to GPCirA locations within the posterior circulation (basilar apex, basilar trunk, vertebrobasilar junction and vertebral artery)
(6) Examine associations between neurological deficits (CND, MD, mRS, hydrocephalus) with GPCirA volume, the amount of brainstem displacement, the occurrence of hydrocephalus and patient age

2.3 Methods

All data outlined below were extracted from the original published article according to the thesis regulation of the Charité Berlin.
For this specific sub-analysis, all imaging and clinical data were extracted retrospectively from the prospective database of the GIA Registry. The GIA Registry is a multicenter observational clinical study collecting prospective clinical and imaging data exclusively on GIA from centers in Europe, USA and Japan. The GIA Registry is registered at ClinicalTrials.gov (registration no. NCT02066493). This study was approved by the ethics committee of the Charité Berlin (EA2/052/08) and by the ethics committees of each participating center. The inclusion criteria into this study were, firstly, that the subjects had one unruptured giant aneurysm (diameter $\geq$ 25mm) located in the posterior circulation and secondly that there was available magnetic resonance imaging before the initiation of any treatment approach.

2.3.1 Patient characteristics

Baseline characteristics, including age and sex, the occurrence of CND, MD and disability (mRS) were extracted from the database of the GIA Registry. The degrees of disability were classified into two categories: (1) mild (mRS 0-2) and (2) severe (mRS 3-5), as previously published (23). In line with international standards motor deficit was defined by insufficient function of a body part or the paralysis of a body part, leading mainly to muscle disorders, such as weakness, loss of muscle control or poor stamina. (International Neuromodulation Society (ins): Motor impairment: reviewed April 2, 2012 Jaimie M. Henderson, Motor deficit Director-at-Large, International Neuromodulation Society, 2011 – 2014 (Accessed August 2, 2017, at http://www.neuromodulation.com/motor-impairment)).

2.3.2 Neuroimaging analysis

In line with previously published studies, all linear measurements were performed on midsagittal T2WI-MRI imaging (4,11). In line with measurements in BI, we defined ΔMT as the distance between the McRL and the highest tip of the GPCirA in an angle of 90 degrees in midsagittal MRI (Figure 1). The McRL is defined as the distance between the basion and the opisthion. Furthermore, we used the Evans Index (EI) to confirm the

presence of hydrocephalus. EI describes the ratio of the transverse diameter of the frontal horns of the lateral ventricles to the maximum inner transverse diameter of the skull at the same axial level in T2WI-MRI (8, 22). The pathological threshold must be larger than 0.3. We also classified the location of the GPCirA, depending on their origin from the arteries of the circle of Willis by using digital subtraction angiography (DSA). GPCirA were allocated into four groups: basilar apex, basilar trunc, vertebrobasilar junction and vertebral artery aneurysms.

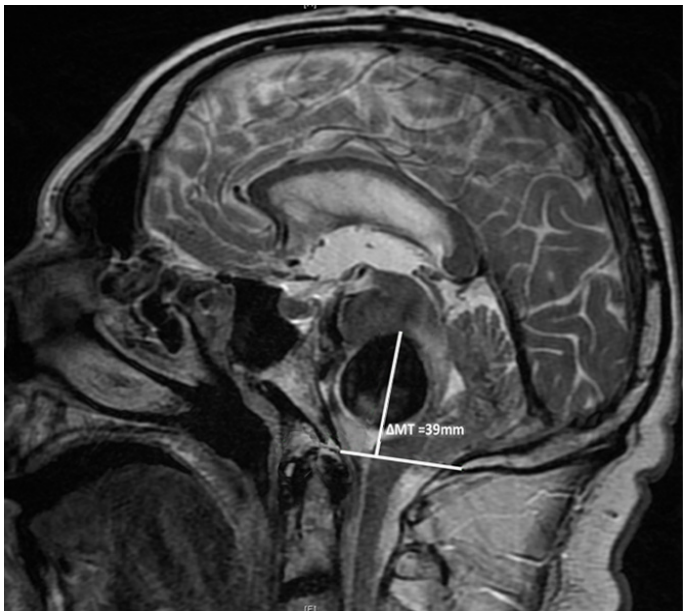

Figure 1: Quantification of brainstem displacement by measuring the distance between the McRae line and the highest tip of the aneurysm (ΔMT)

In order to quantify aneurysm volumes, we used MRI with time-of-flight sequences and T2-weighted images (T2WIs) and digital subtraction angiography (DSA). All volumetric measurements were performed by using the software “iPlan Cranial” (BrainLab, Heimstetten, Germany). Two experienced examiners (P.L., J.D.) conducted the measurements at the GIA registry’s coordinating center at the Charité – Berlin. The circumference of the GPCirA was marked manually using the mouse cursor within each slice of the T2-weighted images. The volumes were then calculated from the software by multiplying the marked areas in each slice with the slice thickness (mean axial thickness 4.3 mm (SD 1.6)). To determine the volume of the thrombosed parts independent of whether PT was intramural or intraluminal, we measured the difference between the perfused GPCirA volume as seen on angiography and the GPCirA volume on MRI.

2.3.3 Statistical analysis

We applied the Shapiro-Will test to examine the distribution of data. Since only patient age was normally distributed, it is presented by means and standard deviation (SD), while the rest of the values is presented as medians with interquartile range (IQR). For the comparison of the baseline data we used Mann-Whitney-U-test for continuous variables or the Chi-square test for categorical data. The Chi-square test was applied to examine the different prevalences of neurological deficits in relation to GPCirA locations in the posterior circulation (basilar apex, basilar trunc, vertebrobasilar junction and vertebral artery). Spearman correlation was used to investigate possible correlations between aneurysm volume and ΔMT. Potential associations were investigated by using binary logistic regression models which examined CND or motoric deficit as dependent variables and patient age, ΔMT, GPCirA volume, and occurrence of hydrocephalus as independent variables. In an ordinal regression model, we tested associations between mRS as dependent variable and patient age, ΔMT, GPCirA volume, occurrence of hydrocephalus and the occurrence of PT as independent variables. In this specific study, we do not present data on interobserver reliability, since previous publications showed that there is a very good interobserver reliability in measuring volumes of giant intracranial aneurysms (25). All statistical analyses were performed using SPSS software, Version 24.0.0.0 (IBM Corp., Armonk, NY, USA).

2.4 Results

MRI and DSA data of 30 unruptured GPCirA in 30 patients, which had been included into the GIA Registry between January 2009 and March 2017 at 7 participating centers, were analyzed in this study. GPCirA and patient characteristics are displayed in Table 1. There was a predominance of the male gender (n=25/30, 83.3%). The mean age was 60.6 years (SD 12.8). 50% of the cases (n=15) presented with CND, 33% (n=10) with MD, while 3 patients were completely asymptomatic (mRS 0, 10.0%). 19 patients (63.3%) had mild disability and 8 patients (26.7%) had severe disability. 17 cases (56.7%) were diagnosed with radiological hydrocephalus. Median GPCirA volume was 7.9 cm^3 (IQR 5.2-14.3) and median diameter was 35.3mm (28.3-39.6mm). Median ∆MT was 41.1 mm (IQR 34.6-51.0). Partial thrombosis was present in 24 cases (80.0%). We found no correlation between ∆MT and aneurysm volume (r_s=0.01; p=0.96).

Table 1: Patient and GPCirA characteristics

Number of patients	30
Number of GPCirA	30
Age, y, (mean, SD)	60.6 (12.8)
Male, n (%)	25 (83.3%)
Cranial nerve deficit, n (%)	15 (50.0%)
Motor deficit deficit, n (%)	10 (33.3%)
mRS-score (mean, SD)	1.8 (2.0)
Asymptomatic (mRS 0), n (%)	3 (10.0%)
Mild disability (mRS 1-2), n (%)	19 (63.3%)
Severe disability (mRS 3-5), n (%)	8 (26,7%)
hydrocephalus, n (%)	17 (56.7%)
∆MT (mm, IQR)	41.1 (34.6-51.0)
GPCirA volume (cm^3, IQR)	7.9 (5.2-14.3)
GPCirA diameter (mm, IQR)	35.3 (28.3-39.6)
Prevalence of PT, n (%)	24 (80.0%)

IQR = interquartile range; SD = standard deviation; ∆MT=distance between McRae-line and highest tip of Giant posterior circulation aneurysm; GPCirA= Giant posterior circulation aneurysms; PT= partial thrombosis

Comparison between CND, MD and mRS groups

Comparing CND groups

Cases with CND were younger (51.0y, SD 21.0) in comparison to those without CND (69.0y, SD 15.0, p=0.01). Furthermore, ∆MT was larger in subjects with CND (50.7mm, IQR 39.2-53.9) compared to subjects without CND (39.0mm, IQR 32.3-45.9, p=0.02). We observed no significant differences between the groups in sex, GPCirA volume or diameters, the prevalence of hydrocephalus or PT and in PT volumes.

Comparing MD groups

There were no significant differences between both MD groups in patient age, sex, prevalence of hydrocephalus or PT, in GPCirA volume and size. Patients with MD had larger ∆MT (50.5mm, IQR 40.8-54.6) in comparison to those without (39.1mm, IQR 32.8-50.5, p=0.04).

Comparing mRS groups

Cases with severe disability (mRS 3-5) displayed larger GPCirA diameters and volumes (diameter: 38.8mm, IQR 35.2-45.6, volume: 14.9 cm^3, IQR 8.6-18.7) compared to cases with mild disability (mRS 0-2) (diameter: 33.2mm, IQR 27.2-37.8, p=0.04, volume: 6.8 cm^3, IQR 4.4-11.7, p=0.03). We found no differences when comparing the two groups regarding sex, age, prevalence of hydrocephalus, prevalence of PT, PT volume or in ∆MT.

Between group differences are summarized in Table 2.

Table 2: Differences in baseline characteristics between patient groups

	Patients with CND (n=15)	Patients without CND (n=15)	p	Patients with motor deficit (n=10)	Patients without motor deficit (n=20)	p	Patients with mRS 0-2 (n=22)	Patients with mRS 3-5 (n=8)	p
Age y (mean, SD)	51 (15.0)	69 (21.0)	0.01	53.3 (26.5)	63.9 (20.8)	0.08	60.5 (20.8)	60.9 (32.0)	0.98
Sex, male, n(%)	14 (93.3)	11 (73.3)	0.14	8 (80.0)	17 (85.0)	0.73	19 (86.4)	6 (75.0)	0.46
Prevalence of hydrocephalus, n(%)	7 (46.7)	10 (66.7)	0.27	7 (70.0)	10 (50.0)	0.30	10 (45.5)	7 (87.5)	0.09
ΔMT (mm, IQR)	50.7 (39.2-53.9)	39.0 (32.3-45.9)	0.02	50.5 (40.8-54.6)	39.1 (32.8-50.5)	0.04	43.5 (34.8-51.0)	41.1 (32.3-65.7)	0.82
GPCirA volume (cm^3, IQR)	6.7 (4.0-10.9)	8.6 (6.6-17.4)	0.16	6.8 (5.3-12.5)	7.9 (4.7-14.7)	0.88	6.8 (4.4-11.7)	14.9 (8.6-18.7)	0.03
GPCirA diameter (mm, IQR)	34.7 (29.0-38.3)	36.5 (28.3-40.6)	1.00	35.6 (31.2-42.7)	34.4 (27.6-39.2)	0.42	33.2 (27.2-37.8)	38.8 (35.2-45.6)	0.04
Prevalence of PT, n (%)	13 (86.7)	11 (73.3)	0.36	9 (90.0)	15 (75.0)	0.33	16 (72.7)	8 (100.0)	0.10

IQR = interquartile range; SD = standard deviation; ΔMT=distance between McRae-line and highest tip of Giant posterior circulation aneurysm; GPCirA= Giant posterior circulation aneurysms; CND= cranial nerve deficit, MD= motor deficit, mRS= modified Rankin Scale; PT= partial thrombosis

GPCirA locations and their relation to neurological deficits

The majority of the GPCirA cases was located at the vertebrobasilar junction (n=12, 40.0%). In 9 cases GPCirA arose from the basilar trunc (30.0%), while 16.7% of the cases had vertebral aneurysms and 13.3% basilar apex aneurysms. We found no differences between GPCirA locations when we compared prevalences of neurological deficits, as displayed in Table 3.

Table 3: Prevalence of neurological deficits in relation to GPCirA locations

Prevalence (%)	GPCirA location				p-value
	Basilar apex (n=4)	Basilar trunc (n=9)	Vertebrobasilar junction (n=12)	Vertebral artery (n=5)	
CND	75.0	55.6	33.3	60.0	0.45
MD	25.0	55.6	25.0	20.0	0.41
mRS 0-2	75.0	77.8	66.7	80.0	0.92

CND= cranial nerve deficit, MD= motor deficit, mRS= modified Rankin Scale

Associations between neurological condition and age, ∆MT, GPCirA volumes, and the occurrence of hydrocephalus

Table 4 displays associations between neurological deficits and patient and aneurysm characteristics. In the binary regression analysis, we found no significant associations between ∆MT, GPCirA volume, patient age or the presence of hydrocephalus and the occurrence of CND or MD. In contrast, when we performed ordinal regression analysis for the mRS groups, we did find that higher degrees of disability according to mRS were significantly associated with larger aneurysm volumes. However, we did not find any further associations with the other examined factors, such as patient age, ∆MT, the occurrence of hydrocephalus or the occurrence of PT.

Table 4: Associations between CND, motor deficits and mRS groups and the examined characteristics

	OR (95% CI)	p
Motor deficit		
∆MT	1.03 (0.893-1.14)	0.58
GPCirA volume	0.96 (0.83-1.10)	0.56
Patient age	0.94 (0.86-1.03)	0.17
Occurrence of hydrocephalus	5.02 (0.46-55.1)	0.19
Cranial nerve deficit		
∆MT	1.04 (0.96-1.13)	0.31
GPCirA volume	0.90 (0.76-1.05)	0.18
Patient age	0.92 (0.84-1.01)	0.08
Occurrence of hydrocephalus	0.69 (0.07-6.49)	0.74
mRS		
∆MT	1.39 (0.97-1.11)	0.34
GPCirA volume	1.13 (1.00-1.27)	**0.04**
Patient age	1.00 (0.93-1.08)	0.99
Occurrence of hydrocephalus	1.13 (0.20-6.35)	0.89
Occurrence of PT	0.11 (0.01-1.17)	0.07

OR= odds ratio; ∆MT= distance between McRae-line and highest tip of giant posterior circulation aneurysm; GPCirA= Giant posterior circulation aneurysms; CI= confidence interval; mRS= modified Rankin Scale

2.5 Discussion

Our analysis of 30 unruptured GPCirA showed that aneurysm volume is a significant predictor for levels of patient disability but not associated with the occurrence of CND or MD. In addition, higher degrees of brainstem displacement away from the cranial base, as measured by the ∆MT, were not a significant risk factor for the prevalence of CND, motor deficit or disability. We observed that neurological deficits occurred in our cohort with high prevalences. In particular, half of our cases presented with CND, 33% with MD and 57% with radiological hydrocephalus. In our patient cohort only 10% of all patients were asymptomatic.

2.5.1 GPCirA and ∆MT

In this study, we primarily hypothesized that certain diagnostic and clinical paradigms used in the diagnosis of BI may be transferrable to GPCirA, since concerning the similar compressive effects directed on the brainstem and the adjacent cranial nerves both neurovascular entities lead to similar radiological and clinical consequences. Chandra et al described 17 cases with BI where the distance between the McRL and the odontoid tip varied from 5.8 mm to a maximal distance of 25.7 mm (3). In their cohort, motor deficit occurred with the highest prevalences (96%) followed by neck pain (62%) and unsteady gait (52%). Cronin et al were the first to establish that the linear measurement of the distance between the McRL and the odontoid is the most valid clinical tool to confirm the diagnosis of BI. They set this distance to be pathological if it is equal or greater than 5mm (4). Furthermore, in another series on 22 cases of BI the distances between McRL and the odontoid tip fluctuated between 3 to 19 mm. Here, the patients mainly presented with motor deficits, neck pain and sensory problems. CND was observed only in 9 cases. In our clinical study on GPCirA, we observed that the distance between the McRL and the highest tip of the aneurysm ranges between 15.9 to 74.7 mm, which is much higher than those observed in series on BI such as the ones mentioned above. This finding suggests that the pathological threshold of 5mm set for BI, cannot be adopted as a pathological one when speaking of giant aneurysms of the posterior circulation. However, we found that not only the amount of brainstem displacement away from the cranial base, but also the degrees of displacement caused by the aneurysm volume, were not significant risk factors for the occurrence of neurological deficits. These findings might support the notion that

these two parameters seem to be two independent risk factors for patient morbidity since they showed no correlations to each other in the examined cases.

2.5.2 GPCirA characteristics and brainstem anatomy

Considering the anatomy of the brainstem, it is known that the brainstem harbors the nuclei of the cranial nerves. Principally, the nuclei of CN IX, X and some sensory nuclei for CN V and VIII are located at the level of the medulla obloganta. The nuclei of CN VI, VII and VIII arise from the pontomedullary junction and the nuclei of CN III and VI from the midbrain tegmentum (21). Taking into account these anatomical relationships, one has to consider that the displacement of the brainstem structures away from the cranial base caused by the compression of the GPCirA may lead to cranial and motor nerve deficits. However, contrary to this assumption, our results suggest that the degrees of brainstem displacement are not a subsequent factor for the occurrence of neurological deficits caused by GPCirA. These surprising findings might indicate that the different levels of craniodorsal displacement of the brainstem cannot affect directly the CN nucleis and the CNs themselves, but they can contribute to higher degrees of patient disability. This notion is supported by the fact that only the aneurysm volume is a significant predictor for severe disability as measured by means of mRS. This phenomenon is in line with previous publications on BI, which report that due to surgical reduction of the odontoid tip the levels of patient disability improved significantly (3, 5).

2.5.3 GPCirA and tumors

Similar findings to the association between disability and aneurysm volume were mentioned in studies on tumors of the posterior fossa. Sekhar et al described 75 cases with clivus meningiomas, of which the vast majority were larger than 2.5 cm. Patients with larger tumor sizes also presented with greater degrees of disability. Larger size of tumors was significantly related to higher risk of disability (20). These results, are similar to ours for GPCirA since the size of a giant aneurysm is at least 2.5 cm such like the sizes presented in the tumor cases above and according to our results, the aneurysmal size is associated with patient disability. In another series on petroclival meningiomas, the surgical removal of the tumors resulted in significant improvement of disability (1).

2.5.4 GPCirA in the literature

In previous published series of 52 vertebrobasilar aneurysms, the aneurysm size, which ranged between 4.0 mm to 35.0 mm, was a significant predictor for the occurrence of brainstem symptoms. However, these symptoms were not specified by the authors (14). In another case series, Xu et al described that patient impairment, as measured by the mRS, was not associated neither with aneurysm size nor with different degrees of brainstem compression (26). The authors categorized the aneurysm into two groups: the first group included aneurysms with a size ≤ 7 mm and the second group included only aneurysms with a diameter greater than 7 mm. They did not describe how many of them were of giant size (26). Concerning these points, we want to stress that none of the studies published so far have systematically investigated risk factors for neurological deficits exclusively for GPCirA. GPCirA have been frequently mentioned only as byproduct of clinical reports on IAs so that their natural course still remains debatable. The findings presented here might differentiate to the clinical reports mentioned above, since we conducted a study exclusively on GPCirA and consequently all of our cases exert larger mass effects on their surrounded structures rather than non-GIA-IA. Furthermore, the occurrence of hydrocephalus is a common co-morbidity in GPCirA and not in smaller intracranial aneurysms and this is why we adjusted our results to the effects of hydrocephalus. Although, in our analysis hydrocephalus occurred with high prevalences, our results showed that it was not associated with the presence of CND, MD or patient disability. So, we may conclude there is a significant disruption of the flow of the cerebrospinal fluid caused by the GPCirA mass effect.

2.5.5 GPCirA, patient age and the occurrence of PT

Interestingly, we found that younger GPCirA patients suffered more frequently from CND. As previously published, the brain volume decreases approximately 5% per decade in patients older than 40 years (18). This age related brain atrophy may create some additional space in brain matter that may be used by the neighboring structures. Thus, some stress on the nuclei may be relieved since there is some more space gained for the adjacent structures.

PT was in our case series a pretty frequent phenomenon. However, we found no associations between PT and neurological deficits. Nevertheless, its effect on the

pathophysiology of the aneurysms still remains uncertain. Different underlying mechanisms have been described to play an important role in the pathogenesis of aneurysm growth. Krings et al and Nasr et al showed that PT was significantly associated with higher rupture and growth rates (13,16). However, PT has also been described to prevent aneurysm rupture as part of remodeling processes within the aneurysms wall (10, 13), which seem to have a protective effect. Furthermore, another result of our analysis is that there was a normal distribution of GPCirA within the posterior circulation ranging from the vertebral artery up to the basilar apex, which shows that every location within the posterior circulation is critical and must be carefully viewed especially when planning treatment.

2.5.6 GPCirA and treatment strategies

In the largest prospective multicenter study on intracranial aneurysms, ISUIA (International Study of Unruptured Intracranial Aneurysms) investigators stated that GPCirA are associated with the highest morbidity and mortality rates, even after surgical or endovascular management (24). They highlighted that both treatment techniques are associated with significant complications resulting in worse clinical outcomes in comparison to giant aneurysms located in the anterior circulation. In our patient cohort about one third was completely asymptomatic or had very mild symptoms. Concerning the high risks of the treatment approaches as stated by ISUIA study group, we feel that conservative management with regular follow up imaging may be an option for patients with no or mild symptoms. It is important to stress that we found that GPCirA volume is the only significant risk factor in predicting neurological deficits. In contrast, none of the frequently discussed risk factors, such as the degree of brainstem displacement away from the cranial base, GPCirA location, the occurrence of PT or of hydrocephalus were associated with the occurrence of neurological deficits or the levels of disability. So, measuring the GPCirA volume may be clinically more relevant since it may help physicians in finding arguments whether initiating intervention is necessary.

2.5.7 Study limitations

There are certain limitations to our analysis. Firstly, we investigated a relatively small number of cases (n=30). Nonetheless, GPCirA are scarce lesions and therefore a multicenter approach was necessary to even gather the number of cases presented here. Another limitation is that we included only the cases with GPCirA from the GIA Registry, for which MRI data was available. According to the study design, the submission of imaging data is optional and thus some cases may be left out of this specific study on GPCirA. Furthermore, we measured as the highest tip of the aneurysm the one presented on midsagittal MRI and one may argue that this may be a random indicator of brainstem displacement. However, we feel that this methodology is rational and transferable to GPCirA since in BI the distance between the McRL and the tip of the odontoid in midsagittal imaging has an established significance. In this analysis we did not examine lateral or medial brainstem displacement. Finally, there might exist a risk of selection bias since patients with neurological deficits may be preferred to be included into the registry rather than asymptomatic cases.

2.5.8 Conclusions

This study is the first to systematically examine the relationship between GPCirA morphology and the occurrence CND, MD and disability. Our results show that GPCirA volume was the only significant predictor of patient disability. Our findings suggest that measuring aneurysm volume maybe essential for deciding whether treatment is crucial or not. Additionally, none of the other examined factors were significantly associated with the occurrence of neurological deficits or with patient disability. Therefore, we feel that our results may indicate that the clinical relevance of examining the degrees of brainstem displacement from the cranial base, measuring PT volumes, defining the exact location of the GPCirA within the posterior circulation or the presence of radiological hydrocephalus may be limited when deciding for or against treatment.

2.6 References

Authors
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1 Almefty R, Dunn IF, Pravdenkova S, Abolfotoh M, Al-Mefty O. True petroclival meningiomas: results of surgical management. J Neurosurg2014 Jan;120:40-51.

2 Bhogal, P, Pérez MA, Ganslandt O, Bäzner H, Henkes H, Fischer S. Treatment of posterior circulation non-saccular aneurysms with flow diverters: a single-center experience and review of 56 patients. J Neurointerv Surg 2017 May; 9: 471-481.

3 Chandra PS, Kumar A, Chauhan A, Ansari A, Mishra NK, Sharma BS. Distraction, compression, and extension reduction of basilar invagination and atlantoaxial dislocation: a novel pilot technique. Neurosurgery 2013 Jun;72:1040-1053.

4 Cronin CG, Lohan DG, Mhuircheartigh JN, Meehan CP, Murphy JM, Roche C. MRI evaluation and measurement of the normal odontoid peg position. Clin Radiol 2007 Sep;62:897-903.

5 Dasenbrock HH, Clarke MJ, Bydon A, Sciubba DM, Witham TF, Gokaslan ZL, Wollinsky JP. Endoscopic image-guided transcervical odontoidectomy: outcomes of 15 patients with basilar invagination. 2012 Feb;70:351-359.

6 Dengler J, Maldaner N, Bijlenga P, Burkhardt JK, Graewe A, Guhl S, Nakamura M, Hohaus C, Kursumovic A, Schmidt NO, Schebesch KM, Wostrack M,

Vajkoczy P, Mielke D. Quantifying unruptured giant intracranial aneurysms by measuring diameter and volume--a comparative analysis of 69 cases. Acta Neurochir (Wien) 2015 Mar;157:361-368.

7 Drake CG, Peerless SJ. Giant fusiform intracranial aneurysms: review of 120 patients treated surgically from 1965 to 1992. J Neurosurg 1997 Aug;87.

8 Evans WA Jr. An encephalographic ratio for estimating ventricular enlargement and cerebral atrophy. Arch Neurol Psychiatry1942;47:931-937.

9 Flemming KD, Wiebers DO, Brown RD Jr, Link MJ, Huston J 3rd, McClelland RL, Christianson TJ. The natural history of radiographically defined vertebrobasilar nonsaccular intracranial aneurysms. Cerebrovasc Dis 2005;20:270-279.

10 Frosen J, Piippo A, Paetau A, Kangasniemi M, Niemelä M, Hernesniemi J, Jääskeläinen J.Remodeling of saccular cerebral artery aneurysm wall is associated with rupture: histological analysis of 24 unruptured and 42 ruptured cases. Stroke 2004 Oct;35:2287-2293.

11 Goel A. Basilar invagination, Chiari malformation, syringomyelia: a review. Neurol India 2009 May-Jun;57:235-46.

12 Kolić Z, Kukuljan M, Vukas D, Bonifačić D, Vrbanec K, Franić IK.Locked-in syndrome in a patient with acute obstructive hydrocephalus, caused by large unruptured aneurysm of the basilar artery (BA). Br J Neurosurg 2017 Dec;31:738-740.

13 Krings T, Alvarez H, Reinacher P, Ozanne A, Baccin CE, Gandolfo C, Zhao WY, Reinges MH, Lasjaunias P.Growth and rupture mechanism of partially thrombosed aneurysms. Interv Neuroradiol 2007 Jun;13:117-26.

14 Mangrum WI, Huston J 3rd, Link MJ, Wiebers DO, McClelland RL, Christianson TJ, Flemming KD. Enlarging vertebrobasilar nonsaccular intracranial aneurysms: frequency, predictors, and clinical outcome of growth. J Neurosurg 2005 Jan;102:72-9.

15 Nakayama Y, Tanaka A, Kumate S, Tomonaga M, Takebayashi S. Giant fusiform aneurysm of the basilar artery: consideration of its pathogenesis. Surg Neurol 1999 Feb;51.

16 Nasr DM, Brinjikji W, Rouchaud A, Kadirvel R, Flemming KD, Kallmes DF. Imaging Characteristics of Growing and Ruptured Vertebrobasilar Non-Saccular and Dolichoectatic Aneurysms. Stroke 2016 Jan;47:106-12.

17 Oishi H, Shimizu T, Nakai K, Miyajima M, Arai H.Successfultreatment of a thrombosedposteriorcerebralarteryaneurysmcausingobstructivehydrocephalus . J Clin Neurosci. 2008 Feb;15:199-202.

18 PetersR.Ageing and the brain. Postgrad Med J 2006 Feb;82:84-8.

19 Pinter NK, McVige J, Mechtler L. Basilar Invagination, Basilar Impression, and Platybasia: Clinical and Imaging Aspects. Curr Pain Headache Rep 2016 Aug;20:49.

20 Sekhar LN, Swamy NK, Jaiswal V, Rubinstein E, Hirsch WE Jr, Wright DC.Surgicalexcision of meningiomasinvolving the clivus: preoperative and intraoperativefeatures as predictors of postoperativefunctionaldeterioration. J Neurosurg 1994 Dec;81:860-8.

21 Smith LH, DeMyer WE. Anatomy of the brainstem. Semin Pediatr Neurol 2003 Dec;10:235-40.

22 Toma AK, Holl E, Kitchen ND, Watkins LD. Evans' index revisited: the need for an alternative in normal pressure hydrocephalus. Neurosurgery 2011 Apr;68:939-44.

23 Weisscher N, Vermeulen M, Roos YB, de Haan RJ. What should be defined as good outcome in stroke trials; a modified Rankin score of 0–1 or 0–2? J Neurol 2008 Jun;255:867-74.

24 Wiebers DO, Whisnant JP, Huston J, 3rd, Meissner I, Brown RD Jr, Piepgras DG Forbes GS, Thielen K, Nichols D, O'Fallon WM, Peacock J, Jaeger L, Kassell NF, Kongable-Beckman GL, Torner JC. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet 2003 Jul 12;362:103-10.

25 Wostrack M, Mielke D, Kato N, Guhl S, Schmidt NO, Maldaner N, Vajkoczy P, Dengler J. Interobserver variability in the characterization of giant intracranial aneurysms with special emphasis on aneurysm diameter and shape. Acta Neurochir (Wien) 2015 Nov;1571859-65.

26 Xu DS, Levitt MR, Kalani MY, Rangel-Castilla L, Mulholland CB, Abecassis IJ, Morton RP, Nerva JD, Siddiqui AH, Levy EI, Spetzler RF, Albuquerque FC, McDougall CG.Dolichoectatic aneurysms of the vertebrobasilar system: clinical and radiographic factors that predict poor outcomes. J Neurosurg2018 Feb;128:560-566.

3 Affidavit-Eidesstattliche Versicherung

„Ich, Pavlina Lenga, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: [Analysis of potential risk factors for the occurrence of brainstem symptoms in subjects with giant intracranial aneurysms of the posterior circulation] selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)“ des ICMJE -*www.**icmje**.org*) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o) und werden von mir verantwortet.
Mein Anteil an der ausgewählten Publikation entspricht dem, der in der untenstehenden gemeinsamen Erklärung mit dem Betreuer, angegeben ist. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o) und werden von mir verantwortet.
Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

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Unterschrift

Berlin, den 28. August 2018

4 Ausführliche Anteilserklärung an der erfolgten Publikation

Lenga P, Hohaus C, Hong B, Kursumovic A, Maldaner N, Bukhardt JK, Bijlenga P, Rufenacht D, Schmidt NO, Vajkoczy P, Dengler J. Giant intracranial aneurysms of the posterior circulation and their relation to the brainstem – analysis of risk factors for neurological deficits. **Journal of Neurosurgery**, Published online August 10, 2018; DOI:10.3171/2018.4.JNS172343.
http://thejns.org/doi/full/10.3171/2018.4.JNS172343

Frau Pavlina Lenga hatte Anteil an folgenden Prozessen im Verlauf der erfolgten Publikation:

1) Literaturrecherche:

-online (v.a. Pubmed): Die Schwerpunkte ihrer Literaturrecherche waren die morphologischen und radiologischen Charakteristika der Aneurysmata des hinteren Stromkreislaufs und deren möglicher Einfluss auf den klinischen Zustand der Patienten. Darüber hinaus hat sie sich auch explizit mit der Literatur beschäftigt, die sich nur auf die Riesenaneurysmata fokussierte, um die Ergebnisse der Doktorarbeit ausführlich interpretieren zu können. Sie hat auch die durch unsere Gruppe publizierten Arbeiten bearbeitet, um ihre Resultate zu bewerten. Da das Thema ihrer Arbeit Messungen aus einer anderen seltenen vaskulären Krankheit, nämlich die Basiläre Invagination, adaptiert hat, hat sie auch intensiv Literatur dafür nachgeforscht, damit sie mögliche Assoziationen zwischen diesen zwei Krankheiten erkennen kann.

2) Datenextraktion:

-Alle klinischen Daten hat sie aus der Datenbank des Giant-Aneurysma-Registers extrahiert. Sie hat nur die Patienten, die ein Aneurysma im hinteren Stromkreislauf hatten, identifiziert und in dieser spezifischen Studie eingeschlossen. Sie hat das Alter, das Geschlecht, den klinischen Zustand anhand der mRS Skala, sowie die neurologischen Defizite (Hirnnervenausfälle und motorische Defizite) für die 30 eingeschlossen Patienten dokumentiert.

3) Datenerhebung:

- In dieser Arbeit hat Frau Lenga die volumetrischen Messungen, d.h. das Aneurysma Volumen sowie das Volumen der partiellen Thrombose mittels des spezialisierten Softwares (iPlan Net, Brainlab) in 3-D-Rekonstruktion erhoben. Sie hat den Aneurysma Durchmesser sowie den ∆MT in der Centricity software gemessen. Zusätzlich hat sie festgestellt, ob die Patienten einen radiologischen Hydrozephalus hatten, indem sie den transversalen Durchmesser der lateralen Ventrikeln und den maximalen transversalen Durchmesser des Schädels gemessen hat. Anhand dieser Messungen hat sie den Evans Index berechnet und die Patienten mit dem radiologischen Hydrozephalus identifiziert. Anschließend hat sie die Aneurysmata anhand der DSA Bildgebung anatomisch zu ihrer dazugehörigen Arterie klassifiziert (basilaris Spitze, basilärer Trunk, vertebrobasiläre Kreuzung und vertebral Arterie).

3) Statistische Analyse:

- Auswertung der Daten mittels Software (SPSS, IBM). Der Shapiro Will Test wurde für die Testung der normalen Verteilung der Daten verwendet. Sie hat zuerst die univariate Analyse durchgeführt, um Unterschiede zwischen den Patienten mit anwesenden und abwesenden neurologischen Defizite in Bezug auf die radiologischen Daten zu finden. Für diesen Zweck hat sie den Chi-square Test für die nominalen Variablen benutzt. Zu den verwendeten nominalen Variablen gehören das Alter, das Geschlecht, die Präsentation von Hydrozephalus und der partiellen Thrombose zu vergleichen. Die kontinuierlichen Variablen (Ay Volumen, Ay Durchmesser und ΔMT) zwischen den unterschiedlichen Gruppen wurden anhand des Mann-Whitney-U Tests getestet. Mögliche Assoziationen zwischen neurologischen Defizite und dem Ay Volumen, dem ΔMT, und der Präsentation von Hydrozephalus und der partiellen Thrombose wurden von Frau Lenga mittels der multivariablen Regressionsanalyse ermittelt.

4) Dateninterpretation und Erstellung des Manuskriptes:

-Frau Lenga hat anhand der statistischen Auswertung ihrer Messungen, ihrer dokumentierten klinischen Patienten-Daten sowie Ihrer Literaturrecherche den ersten Entwurf inklusive Graphiken und Tabellen fertiggestellt. Sie hat dann anhand der Kommentare der Co-Autoren den zweiten Entwurf bearbeitet und diesen in den Journal of Neurosurgery eingereicht.

Nach Einarbeitung der Kommentare der Reviewer (Journal of Neurosurgery) hat sie die finale Version ihrer Doktorarbeit fertiggestellt.

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Unterschrift der *Doktorandin*

5 Auszug aus der Journal Summary List (ISI Web of Knowledge)

https://intranet.charite.de/fileadmin/user_upload/microsites/sonstige/medbib/Impact_Faktoren_2017/ISI-WEB-Liste-Kategorie-Surgery.pdf **(Nummer: 14, Journal of Neurosurgery)**

Journal Data Filtered By: **Selected JCR Year: 2017** Selected Editions: SCIE,SSCI
Selected Categories: **"SURGERY"** Selected Category Scheme: WoS
Gesamtanzahl: 200 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	ANNALS OF SURGERY	48,932	9.203	0.066340
2	JAMA Surgery	4,515	8.498	0.024940
3	JOURNAL OF HEART AND LUNG TRANSPLANTATION	11,129	7.955	0.028970
4	JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY	29,695	7.144	0.032980
5	ENDOSCOPY	10,185	6.629	0.017400
6	AMERICAN JOURNAL OF TRANSPLANTATION	23,460	6.493	0.051290
7	AMERICAN JOURNAL OF SURGICAL PATHOLOGY	20,873	5.878	0.023060
8	BRITISH JOURNAL OF SURGERY	22,899	5.433	0.031220
9	JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY	27,492	4.880	0.042650
10	JOURNAL OF THE AMERICAN COLLEGE OF SURGEONS	16,326	4.767	0.031690
11	JOURNAL OF BONE AND JOINT SURGERY-AMERICAN VOLUME	46,966	4.583	0.044930
12	NEUROSURGERY	28,592	4.475	0.025930
13	ARTHROSCOPY-THE JOURNAL OF ARTHROSCOPIC AND RELATED SURGERY	15,568	4.330	0.020760
14	JOURNAL OF NEUROSURGERY	34,561	4.318	0.030750
15	CLINICAL ORTHOPAEDICS AND RELATED RESEARCH	40,313	4.091	0.037880
16	TRANSPLANTATION	24,731	3.960	0.030960
17	Surgery for Obesity and Related Diseases	5,351	3.900	0.011660
18	OBESITY SURGERY	12,135	3.895	0.018350
19	EUROPEAN JOURNAL OF VASCULAR AND ENDOVASCULAR SURGERY	8,352	3.877	0.012910
20	ANNALS OF SURGICAL ONCOLOGY	26,592	3.857	0.053440

1

Selected JCR Year: 2017; Selected Categories: "SURGERY"

6 Druckexemplar

Lenga P, Hohaus C, Hong B, Kursumovic A, Maldaner N, Bukhardt JK, Bijlenga P, Rufenacht D, Schmidt NO, Vajkoczy P, Dengler J, Giant intracranial aneurysms of the posterior circulation and their relation to the brainstem – analysis of risk factors for neurological deficits, **Journal of Neurosurgery**, Published online August 10, 2018; DOI:10.3171/2018.4.JNS172343.

http://thejns.org/doi/abs/10.3171/2018.4.JNS172343

7 Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

8 Komplette Publikationsliste

Lenga P, Hohaus C, Hong B, Kursumovic A, Maldaner N, Bukhardt JK, Bijlenga P, Rufenacht D, Schmidt NO, Vajkoczy P, Dengler J, Giant intracranial aneurysms of the posterior circulation and their relation to the brainstem – analysis of risk factors for neurological deficits, J Neurosurg 10 Aug 2018 (Impact Factor 4.318)

Durner G, Piano M, Lenga P, Mielke D, Hohaus C, Guhl S, Maldaner N, Burkhardt JK, Pedro MT, Lehmberg J, Rufenacht D, Bijlenga P, Etminan N, Krauss JK, Boccardi E, Hänggi D Vajkoczy P, Dengler J. Cranial nerve deficits in giant cavernous carotid aneurysms and their relation to aneurysm morphology and location. Acta Neurochir (Wien). 2018 Aug;160(8):1653-1660 (Impact Factor 1.929)

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Als nächstes möchte ich mich bei Prof Dr. Peter Vajkoczy und bei allen Mitgliedern des Riesenaneurysma-Registers für ihre Mitarbeit bedanken. Ohne die Studiengruppe hätte ich keine Chance gehabt, meine Doktorarbeit zu verwirklichen.

Auch möchte ich meinem Bruder, Niko, für seine ständige Unterstützung und Förderung danken. Zuletzt danke ich meiner Mutter und meinem Vater, die zwar tausende Kilometer entfernt, aber gefühlt immer bei mir waren.