Acta Neurochirurgica (2018) 160:1653–1660
https://doi.org/10.1007/s00701-018-3580-2

ORIGINAL ARTICLE - VASCULAR

Cranial nerve deficits in giant cavernous carotid aneurysms and their relation to aneurysm morphology and location

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Received: 7 March 2018 / Accepted: 30 May 2018 / Published online: 9 June 2018

Abstract

Background Giant cavernous carotid aneurysms (GCCAs) usually exert substantial mass effect on adjacent intracavernous cranial nerves. Since predictors of cranial nerve deficits (CNDs) in patients with GCCA are unknown, we designed a study to identify associations between CND and GCCA morphology and the location of mass effect.

Methods This study was based on data from the prospective clinical and imaging databases of the Giant Intracranial Aneurysm Registry. We used magnetic resonance imaging and digital subtraction angiography to examine GCCA volume, presence of partial thrombosis (PT), GCCA origins, and the location of mass effect. We also documented whether CND was present.

Results We included 36 GCCA in 34 patients, which had been entered into the registry by eight participating centers between January 2009 and March 2016. The prevalence of CND was 69.4%, with one CND in 41.7% and more than one in 27.5%. The prevalence of PT was 33.3%. The aneurysm origin was most frequently located at the anterior genu (52.8%). The prevalence of CND did not differ between aneurysm origins ($p = 0.29$). Intracavernous mass effect was lateral in 58.3%, mixed medial/lateral in 27.8%, and purely medial in 13.9%. CND occurred significantly more often in GCCA with lateral (81.0%) or mixed medial/lateral (70.0%) mass effect than in GCCA with medial mass effect (20.0%; $p = 0.03$). After adjusting our data for the effects of the location of mass effect, we found no association between the prevalence of CND and aneurysm volume (odds ratio (OR) 1.30 (0.98–1.71); $p = 0.07$), the occurrence of PT (OR 0.64 (0.07–5.73); $p = 0.69$), or patient age (OR 1.02 (95% CI 0.95–1.09); $p = 0.59$).

Conclusions Distinguishing between medial versus lateral location of mass effect may be more helpful than measuring aneurysm volumes or examining aneurysm thrombosis in understanding why some patients with GCCA present with CND while others do not.

Clinical trial registration no. NCT02066493 (clinicaltrials.gov)

Portions of this work were presented in a talk at the annual meeting of the European Association of Neurosurgical Societies/Vascular Section in Nice, France, on September 9, 2017.

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Keywords Giant intracranial aneurysms · Cavernous carotid aneurysm · Aneurysm volume · Partial thrombosis

Introduction

Giant cavernous carotid aneurysms (GCCAs) are rare entities [1, 2, 21]. They usually cause substantial mass effect and compression of adjacent intracavernous cranial nerves (CNs), resulting in symptoms such as ophthalmoplegia or facial pain [6, 14]. So far, there is no systematic examination of potential risk factors for CN deficit (CND) in patients with GCCA. Previously published case series describe that some patients with GCCA present with CND while others do not without further analysis of potential reasons for this difference [6, 10, 11, 14]. In non-giant cavernous carotid artery aneurysms, the occurrence of CND was shown to be determined by the segment of the cavernous carotid artery harboring the aneurysm [11]. Such an association may be difficult to establish in GCCA, since they are so large that they usually incorporate all segments of the cavernous carotid artery (CCA) instead of only one. In other tumorous lesions within the cavernous sinus, classifications according to the exact location of mass effect are common. As an example, intracavernous hemangiomas have recently been classified according to the location of their mass effect in relation to the carotid artery as medial versus lateral [18]. Since, so far, there is no comparable categorization of the location of mass effect in GCCA, one can only assume that since most cranial nerves within the cavernous sinus are located at the lateral sinus wall, lateral aneurysm mass effect may increase the odds of CND. Furthermore, it remains uncertain whether larger GCCA may be more likely to cause CND that their smaller counterparts. The identification of potential risk factors for CND in GCCA, including the exact location of intracavernous mass effect and aneurysm volume, may be important when discussing the morbidity of GCCA.

We designed a study in which we used current data from the Giant Intracranial Aneurysm (GIA) Registry's clinical and imaging databases with the aim to identify potential predictors of CND in patients with GCCA with emphasis on different aneurysm origins, morphologies, volumes, and locations of mass effect. Our main hypothesis was that in patients with GCCA, CND may be more likely in patients with larger GCCA volumes and in GCCA with lateral rather than medial mass effect.

Methods

All results presented in this paper are based on a retrospective analysis of the GIA Registry's prospective clinical and imaging databases. Patient data included into this specific study were entered into the GIA Registry by eight participating centers between January 2009 and March 2016. The GIA Registry is an international prospective multicenter study collecting clinical and imaging data exclusively on GIA. The members of the GIA Study Group are listed in the Appendix. Data collection was approved by the ethics committee of the GIA Registry's coordinating center at the Charité, Berlin (EA2/052/08), and by the ethics committees of all participating centers. Informed consent was obtained from all participants included in the Registry, which is listed at clinicaltrials.gov under the registration number NCT02066493. Inclusion criteria for this specific analysis were the diagnosis of an unruptured GIA originating from the internal carotid artery's cavernous segment, which was defined as cranial to the petrous ICA segment and caudal to the origin of the ophthalmic artery. Another inclusion criterion was the existence of magnetic resonance imaging (MRI) of the GCCA before any treatment.

Neuroimaging and GIA characteristics

All cases were examined using T2-weighted magnetic resonance imaging (MRI) and time-of-flight sequences or regular MR-angiography to analyze perfused parts of the aneurysms and vessels. If available, information from digital subtraction angiography (DSA) was added. Both intraluminal and intramural thrombus were declared part of the GCCA. We also measured the volumes of perfusion and partial thrombosis (PT) and located GCCA origins within the cavernous carotid artery. Aneurysm origins were categorized according to the anatomical segment of the cavernous carotid artery harboring the inflow into the aneurysm (posterior genu, horizontal segment, or anterior genu). The location of GCCA mass effect was described using categories previously established for the localization of cavernous hemangiomas as medial, lateral, and mixed medial/lateral according to the position of mass effect in relation to the internal carotid artery on a coronal reconstruction image of the cavernous sinus (Fig. 1) [18]. Medial location was documented if the mass effect was located medially to the cavernous carotid line, lateral when laterally and mixed medial/lateral when the mass effect extended to both sides of the cavernous carotid line.

All imaging was analyzed at the GIA Registry's coordinating center at the Charité-Berlin by two experienced examiners (GD, JD) using the software "iPlan Cranial" (BrainLab, Heimstetten, Germany). Both examiners manually marked the circumference of the objects of interest within each slice of the MRI. The software then calculated the objects' volumes with respect to slice thickness.

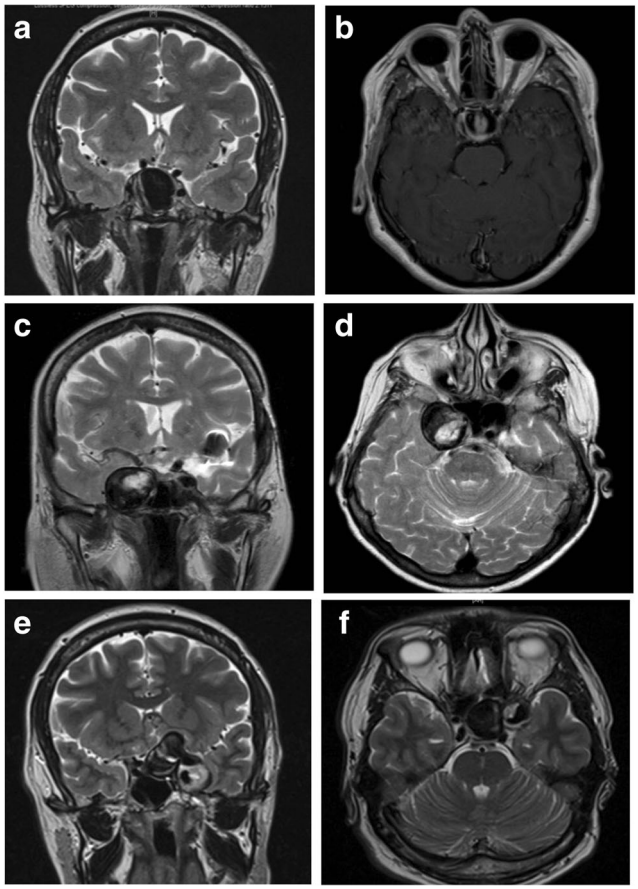

Fig. 1 Representative MRI in three cases of each type of intracavernous mass effect. The location of mass effect was categorized in relation to the cavernous carotid artery, as medial type (**a**, **b**), lateral type (**c**, **d**) or mixed medial/lateral type (**e**, **f**), as previously described by Tang et al.

Clinical characteristics

Patient and clinical characteristics included patient age, sex, and the occurrence of CND. If a CND was present, the including registry center was contacted and asked to specify how many and which cranial nerves were affected, since this differentiation is not made by the registry's case report forms.

Statistical analysis

Since all imaging characteristics were measured by two examiners independently, interobserver agreement was calculated using the two-way random-effects model intraclass correlation test. Since we found good to excellent interobserver reliability concerning all measurements and previous reports have already stated that GIA size and location are assessed with good to excellent interobserver reliability, the results of this analysis are not shown. The Shapiro–Wilk test was used to test variables for normal distribution and normally distributed values are given as means with standard deviation (SD), not normally distributed values as medians with 95% confidence intervals (CIs). Baseline characteristics were compared using the Mann-Whitney *U* test or chi-square test. The relation between the presence of PT or CND and GCCA origins and locations of mass effect was tested using the chi-square test. A binary logistic regression model was applied to test for associations between CND as dependent variable and patient age, GCCA volume and the prevalence of PT as independent variables with adjustment for the effects of the location of mass effect. The regression model fit was tested using omnibus testing of model coefficients, the Nagelkerke R-square and separate accuracy of classification tests of actual versus predicted values. All statistical analyses were performed using SPSS software, version 24.0.0.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

We included 36 unruptured GCCA in 34 patients (Table 1). Mean patient age was 58.9 years (SD 14.8), and there was a predominance of the female sex (31/35, 86.1%). A CND was present in 69.4% of all GCCA, with one CND in 41.7% and 2 or more in 27.5%. The prevalence of PT was 33.3%.

GCCA origins and intracavernous locations of mass effect

We categorized all GCCA according to their vascular origin and intracavernous mass effect (Table 2). Anterior genu origin was found in the majority of cases (52.8%). GCCA mass effect was lateral in 21 cases (58.3%) while a mixed medial/lateral type was found in 10 cases (27.8%) and purely medial location in only 5 cases (13.9%). The most frequent combination was origin from the anterior genu of the cavernous ICA and lateral mass effect (9/36 = 25.0%). We found that lateral (9.0 cm^3; $p = 0.03$) and mixed medial/lateral types (13.1 cm^3) were significantly larger in volume than medial GCCA (6.2 cm^3; $p = 0.02$).

CND and PT in relation to different GCCA origins and locations of mass effect

There were no differences in the prevalence of CND or PT between the different vascular origins of GCCA ($p = 0.11$ and $p = 0.17$). However, CND was significantly more frequent in lateral (81.0%) and mixed lateral-medial types (70.0%) than in the medial type (20.0%; $p = 0.03$). We also found a trend towards more frequent PT in lateral (28.6%) and mixed lateral-medial types (60.0%) than in medial GCCA (0%). However, this trend barely missed statistical significance ($p = 0.052$). Table 3 displays the prevalence of CND per GCCA origins and locations of mass effect.

Table 1 Patient and aneurysm characteristics

Number of GIA	36
Age (mean, SD)	58.9 (14.8)
Female, *n* (%)	31 (88.6%)
CN-deficit, *n* (%)	25 (69.4%)
Number of affected CN, *n* (%)	
None	11 (30.6%)
One	15 (41.7%)
Multiple	10 (27.8%)
Paresis of CNs, *n* (%)	25 (69.5%)
III	4/25 (16.0%)
VI	11/25 (44.0%)
III, VI	3/25 (12.0%)
III, IV, VI	2/25 (8.0%)
III, IV, VI, V	5/25 (20.0%)
Ay-Volume (cm^3, median, IQR)	8.8 (6.5)
Cases with partial thrombosis (*n*, %)	12 (33.3%)
Volume of PT (cm^3, median, IQR)	5.1 (9.1)

CN cranial nerve, *GCCA* giant cavernous carotid aneurysms, *PT* partial thrombosis

CND in relation to GCCA volume, PT, and patient age

Since CND was significantly more frequent in lateral and mixed lateral-medial types, we adjusted our data for the effects of the location of mass effect when examining factors associated with CND (Table 4). There was no association between the prevalence of CND and aneurysm volume (OR 1.30 (0.98–1.71); $p = 0.07$) or the occurrence of PT (OR 0.64 (0.07–5.73); $p = 0.69$), or patient age (OR 1.02 (95% CI 0.95–1.09); $p = 0.59$).

Discussion

Clinical evidence on GCCA is scarce and usually views GCCA as a homogeneous group without differentiating between specific locations of mass effect or other morphological features. Previous case series have described that some patients with GCCA present with CND while others do not, yet no attempts have been undertaken to identify underlying mechanisms [10, 11, 15, 17]. To our knowledge, our study is the first to examine risk factors for CND in GCCA. Our main result is that the prevalence of CND was not associated with GCCA volumes and that CND was more frequent if the aneurysm's mass effect was lateral or mixed lateral-medial compared to only medial. We also found that there was no difference in the prevalence of CND between different vascular aneurysm origins within the cavernous ICA segment.

Table 2 Relation between GCCA origins and location of mass effect

	Location of mass effect		
Origin of GCCA	Medial $n = 5$	Lateral $n = 21$	Mixed $n = 10$
Posterior genu, $n = 3$	0	1	2
Horizontal, $n = 8$	0	6	2
Anterior genu, $n = 19$	5	9	5
All segments, $n = 6$	0	5	1

GCCA giant cavernous carotid aneurysms

Aneurysms of the CCA are a unique subcategory of intracranial aneurysms, since they are usually separated from the brain by the dura of the cavernous sinus and therefore rarely cause subarachnoid hemorrhage. Their prognosis is more benign than that of all other intracranial aneurysms. In GCCA, the 5-year rupture rate is relatively low (6.4%) compared to that of giant intracranial aneurysms at other locations (40.0–50.0%) [21]. Still, GCCA usually exert substantial mass effect on their surroundings. It is therefore somewhat surprising that in our series, GCCA volumes were not associated with the occurrence of CND. This may be explained by the fact that we only included giant size aneurysms and that, once the size threshold of 25 mm is surpassed, differences in aneurysm size may be less relevant than in CCA aneurysms smaller than 25 mm.

The fact that we identified strictly medial location of the mass effect as least likely to cause CND is best explained by the anatomical structure of the cavernous sinus. CN III, IV, and the first two divisions of CN V are located within the lateral sinus wall, and only CN VI traverses the sinus medially while CN II is located medially above the roof of the sinus [4, 7]. Lateral mass effect may therefore increase the risk of CND since the largest group of cavernous sinus-associated CN is located in the lateral wall while strictly medial mass effect may affect a smaller group of CN. In addition to direct compression of nerval structures, it seems plausible that the arteries supplying the intracavernous CN may be compressed as well, mainly the inferolateral arterial trunk, which arises from the CCA and supplies not only the CN but also the Gasserian ganglion and the dura of the cavernous sinus [4]. In contrast, purely medial mass effect may less likely affect CN III–VI but exert pressure mainly on CN II and the pituitary gland directly as well as on the capsular arteries of McConnell, which supply the gland. [7]

In our series, we found a prevalence of CND of 69.4%, which highlights that CND is a common phenomenon in patients with GCCA. Interestingly, these results are comparable to those of most published series that predominantly included non-giant CCA aneurysms. Linskey et al. describe a series of 44 CCA aneurysms, of which only 7 were GCCA, and identified CND in 57% of all cases [11]. Vasconcellos et al. present data on 40 CCA aneurysms, of which 10 were GCCA. They observed CND in 83% of all cases [20]. Kupersmith et al. describe 79 CCA aneurysms, without specifically mentioning how many were GCCA, and found that 74.7% presented with CND [10]. Stiebel-Kalish et al. examined 185 CCA

Table 3 Prevalence of CND per GCCA locations and origins of mass effect

	Patients with CND ($n = 25$)	Patients without CND ($n = 11$)	p value
Vascular origin			
Posterior genu, $n = 3$	2 (66.7%)	1 (33.3%)	0.29
Horizontal segment, $n = 8$	8 (100.0%)	0 (0.0%)	
Anterior genu, $n = 19$	11 (57.9%)	8 (42.1%)	
All segments involved, $n = 6$	4 (66.7%)	2 (33.3%)	
Location of mass effect			
Medial, $n = 5$	1 (20.0%)	4 (80.0%)	0.03
Lateral, $n = 21$	17 (81.0%)	4 (19.0%)	
Mixed, $n = 10$	7 (70.0%)	3 (30.0%)	

CND cranial nerve deficit, *GCCA* giant cavernous carotid aneurysms

aneurysms, again without mentioning the proportion of GCCA, and they found CND in 65% of their cases [17]. The lowest prevalence of CND in CCA aneurysms was described by Rosi Jr. et al. who examined 123 CCA aneurysms, of which 32.5% were GCCA [15]. In their series, only 27% presented with CND. The fact that the prevalence of CND in our series of GCCA is comparable to that of most series on predominantly non-giant CCA aneurysms further suggests that CND may not be associated with aneurysm volume but rather with the location of mass effect. It is also worth pointing out that when comparing patients with one to those with multiple CND we found no differences in GIA volume between both groups.

Another finding of our analysis was that PT was not associated with the occurrence of CND. The physiological role of PT remains controversial, as it was shown to increase the risk of aneurysm rupture and growth [9, 12] as well as to exert a protective effect against aneurysm rupture as part of a remodeling process within the aneurysm wall [5, 9]. In a series of 40 CCA aneurysms, Vasconcellos et al. describe that five thrombosed spontaneously, after which trigeminal pain symptoms decreased significantly [20]. In contrast, Kupersmith et al. hypothesize that PT of CCA aneurysms may be associated with the occurrence of CND, yet they do not present systematic data to corroborate this argument [10]. In a previous examination of patients included in the GIA Registry, we found that in GIA outside of the cavernous sinus PT increased the risk of perianeurysmal cerebral edema, while PT in GCCA produced no perianeurysmal edema, even though substantial mass effect on the temporal lobe was observed in the majority of GCCA cases [1]. This difference was explained by the fact that in GCCA, the dura of the cavernous sinus wall may protect the brain from edema formation by shielding it from toxins produced by the thrombus. To explain why PT may not have had an effect on the prevalence of CND in our series, a similar argument may be made since CN III, IV, and the first two divisions of CN V course through the lateral wall of the cavernous sinus, more exactly between the outer layer (dura propria) and an inner membranous layer of the wall [19]. This inner membranous layer may directly shield the CN from the thrombosed parts of the GCCA.

Table 4 Associations between the occurrence of CND and patient age, GCCA volumes, and the prevalence of PT after adjusting for the effects of the location of mass effect

	Coefficient	SE	OR (95% CI)	p value
Patient age	0.02	0.04	1.02 (0.95–1.09)	0.59
GCCA volume	0.26	0.14	1.30 (0.98–1.71)	0.07
PT	− 0.44	1.12	0.64 (0.07–5.73)	0.69

GCCA giant cavernous carotid aneurysms, *OR* odds ratio, *PT* partial thrombosis, *SE* standard error

The findings of our study are clinically relevant since they suggest that larger GCCA volumes themselves may not be useful arguments for or against GCCA treatment. This is especially important since cavernous carotid aneurysms rarely cause subarachnoid hemorrhage and therefore the risk of rupture is not as important for the assessment of the urgency of interventional treatment as it is in noncavernous intracranial aneurysms. [4] Since, so far, the role of different GCCA volumes has not been studied systematically, larger cavernous carotid aneurysm volumes and sizes have somewhat anecdotally been viewed as relevant when deciding on whether to treat conservatively or not [4]. In this context, it is of note that both endovascular and surgical GCCA therapy are associated with a relevant likelihood of treatment-associated ischemic complications. In a series of large and giant cavernous carotid aneurysms that were treated endovascularly by placement of flow-diverters with or without additional coils, postinterventional complications occurred in 15.9% of all cases, most of which showed symptoms of cerebral ischemia [13]. Similar complication rates were described for surgical treatment of large or giant cavernous carotid aneurysms, which usually consists of proximal aneurysm occlusion with or without a cerebrovascular bypass [3, 4, 8, 16]. Even in experienced hands, the prevalence of postoperative ischemia can reach 17% [16]. In clinical routine, our results

may add to the discussion on whether certain GCCA ought to be treated conservatively or nonconservatively. Our findings suggest that the frequently supposed urgency of nonconservative GCCA treatment, even in patients with no or only mild symptoms, should be reconsidered based on the exact location of mass effect within the cavernous sinus, which was the only significant predictor of neurological deficits before any type of treatment in our analysis.

The main strength of our analysis is that it is the first to systematically examine the relationship between GCCA characteristics and the occurrence of CND. However, certain limitations exist. The overall number of cases included in this analysis may seem limited. However, since GCCA are extremely rare entities, a multicenter approach was necessary in order 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. The resulting nonconsecutive inclusion into this specific study may serve as a potential bias. Also, we did not include any follow-up data or data on treatment outcome, since the GIA registry is still ongoing and any follow-up data will be analyzed in the future.

Conclusions

The prevalence of CND was not associated with different GCCA volumes or partial aneurysm thrombosis. We found that CND was significantly more frequent in GCCA with lateral location of mass effect compared to those with medial mass effect. Distinguishing between medial versus lateral location of mass effect may be more helpful than measuring aneurysm volumes or examining aneurysm thrombosis in understanding why some patients with GCCA present with CND while others do not.

Acknowledgements The authors would like to thank all members of the Giant Intracranial Aneurysm Group.

Funding The Giant Intracranial Aneurysm Registry is funded by the Center for Stroke Research-Berlin (Grant No. CS-2009-12) to JD, the coordinating officer of the registry. The sponsor had no role in the design or conduct of this research.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. Dr. Nima Etminan is a member of Medical monitor and steering committee NEWTON 2 and received Research grant PROTECT-U, which are unrelated to the present study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Appendix

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