TABLE 6. Haplotype Association Study With Adjustment for Covariates by THESIAS (the Third Cohort)

Haplotype Identification Code	Haplotype Sequence	Frequency of Haplotype: Unrelated Case	Frequency of Haplotype: Control	OR (95% CI)	*P*
H1	GACC	0.211	0.268	0.69 (0.52–0.92)	0.012*
H2	GACT	0.117	0.131	0.82 (0.57–1.18)	0.29
H3	GCCC	0.251	0.215	1.11 (0.79–1.42)	0.70
H4	TCTC	0.289	0.271	Intercept	
Covariate					
Sex (female vs male)				2.26 (1.55–3.30)	0.000024
Hypertension				1.97 (1.44–2.70)	0.000027
Smoking (ever-smoker vs nonsmoker)				1.64 (1.12–2.42)	0.011864
Alcohol (ever-drinker vs nondrinker)				0.91 (0.63–1.33)	0.63

*After Bonferroni correction, P_{corr}=0.048.

IA, which implies that the penetrance of IA is not as complete as was expected.[24,25] Finally, case-control studies using sequence variants revealed a protective haplotype (GACC) against the most common haplotype (TCTC). With these lines of evidence, *TNFRSF13B* emerges as a candidate for susceptibility for IA.

Transmembrane activator and calcium modulator ligand interactor (TACI) encoded by *TNFRSF13B* mediates isotype switching in B cells. The mutations in *TNFRSF13B* have recently been reported to be associated with common variable immunodeficiency (CVID) and immunoglobulin A (IgA) deficiency in humans.[26,27] In 1 of these studies, 11 mutations (4.1%) were found in 270 chromosomes from 135 sporadic CVID cases.[26] It is of particular interest that most sporadic cases with CVID had only 1 mutant allele, which suggests a mechanism of gain of function or haploinsufficiency.

Given that mutations of *TNFRSF13B* are associated with CVID or IgA deficiency, an unanswered question is why variants in *TNFRSF13B* are associated with IA. It is interesting that in the present study, 12 of 17 rare variants in IA cases and 3 of 5 rare variants in control subjects were found in the CRD2 domain, whereas the majority of mutations in cases with CVID or IgA deficiency were found at the C terminal side to the CRD2 region, which transfers signals from cell surface to intracellular domains. We postulate that variants at the ligand binding site may cause quantitative changes, whereas mutations in signal transduction result in qualitative changes. Different modes of functional impairments might be associated with different phenotypes. Studies are needed to investigate this further.

In the present study, we found 3 nonsense mutations (1 stop codon, 1 splicing acceptor site change, and 1 frame shift) and 5 rare nonsynonymous changes in 17 cases. Each case had a single variant. It is interesting that these variants are novel, and none were found in whites.[26,27] The most common mutation among Japanese with IA is G76S (8/17), whereas in whites with CVID, it is A181E, which suggests founder mutations that are specific to ethnic groups. If this is true, genetic preposition to IA or CVID or IgA deficiency may be predicted by these founder mutations in the future.

The present study has several limitations. First, population-attributable risks of IA are calculated to be 7% to 10%, whereas that of smoking observed is ≈24%, which suggests that the risk attributable to *TNFRSF13B* is approximately one third that of smoking in the present cohort. However, further studies are needed, because only a small fraction of the risk is explained by *THNFRS13B*. Second, we have selected only 9 genes as the primary gene set from 108 genes. We excluded genes for which the functions are not well characterized or those with well-characterized functions that are not considered to be involved in IA. Although this is primary screening, this study cannot be free from selection bias. In the next study, we are expanding the gene set so that it includes some genes with unknown functions. Third, we tested with PolyPhen whether or not nonsynonymous variants were functional. Bioinformatics approaches may sometimes be misleading.[28] In the future, we should explore other genes that had "possibly damaging" or "unknown" variants. Effects of variants on the function of TACI should also be confirmed experimentally in future. Fourth, there may be an argument for the hypothesis that rare variants contribute to common diseases. However, the hypothesis can provide criteria for positive selection of a susceptibility gene, which would have been overlooked by a haplotype-based association study. Fifth, in the present study, we did not determine CVID-related parameters such as B-cell expression of TACI and serum levels of immunoglobulin. Finally, we did not explore genes in LD with *TNFRSF13B*. The International HapMap Project (http://www.hapmap.org) suggests that there is LD between *LOC96597* and *TNFRSF13B*. Further exploration of this will be needed in the future.

With positive findings, the above rationale, and reasonable background, we proposed that *TNFRSF13B* is one of the candidate genes for susceptibility for IA, notwithstanding several limitations. This in turn proposes that immunologic mechanisms may play a role in IA development to a discernible extent. Our hypothesis is in accordance with clinical experiences in which IA is often found in subjects with autoimmune diseases.[29,30] Further studies are needed to strengthen our hypothesis. In addition, the present results might pave the way for an investigation of a link between immunologic events and IA development.

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Disclosures

None.

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CLINICAL PERSPECTIVE

A number of genetic studies conducted on familial intracranial aneurysms (IA) have reported positive findings for various chromosomal regions, including 1p, 2p, 7cent, 17cent, 19q and Xp. In the present study, we have extensively searched for genes on chromosome 17cent. A total of 9 candidate genes (*TNFRSF13B, M-RIP, COPS3, RAI1, SREBF1, GRAP, MAPK7, MFAP4*, and *AKAP10*) were selected from 108 genes within this linked region. *TNFRSF13B* was the only gene tested that was associated with intracranial aneurysms in the 58 cases (29 pedigree probands and 29 unrelated non-pedigree cases). The association of IA with *TNFRSF13B* was further studied in 304 unrelated cases and 332 control subjects. In unrelated cases, deleterious or nonsynonymous variants were found at a higher frequency (2.3%) than in control subjects (0.8%) (P=0.035). The association study using single nucleotide polymorphisms in an unrelated case-control cohort revealed a protective haplotype (odds ratio=0.69, 95% confidence interval, 0.52 to 0.92;K p=0.012) to the major haplotype. We propose that *TNFRSF13B* is one of the genes which determine susceptibility for IAs. Other genes are also involved in IAs, as the population attributable risk of *TNFRSF13B* is small (7% to 10%). Interestingly, *TNFRSF13B*, one of the members that transduces key signals in the regulation for the survival and the apoptosis of immune cells, has recently been reported to be associated with common variable immunodeficiency and IgA deficiency. The present finding provides support for the hypothesis that immunological mechanisms play a role in the development of IA.

Optic Strut as a Radiographic Landmark in Evaluating Neck Location of a Paraclinoid Aneurysm

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OBJECTIVE: The optic strut (OS) is a candidate landmark in computed tomographic (CT) angiographic scans for the discrimination of intradural and extradural/intracavernous aneurysms involving the paraclinoid segment of the internal carotid artery. The goal of this study is to examine and confirm the qualifications of the OS as a landmark in CT angiographic scans for the preoperative evaluation of aneurysms in this region.

METHODS: Seventeen consecutive patients with 18 unruptured paraclinoid aneurysms who underwent preoperative CT angiography scans and direct surgery between 1998 and 2005 were evaluated retrospectively. We focused on the relationships of the necks of aneurysms to the OS in CT angiographic scans and that of the necks to proximal dural rings during intraoperative examinations.

RESULTS: Direct surgery revealed that 14 aneurysms, the necks of which were distal to the OS on CT angiographic scans, arose distal to the proximal dural rings. All aneurysms were clipped, except one exhibiting calcification of the neck. Three aneurysms, for which the neck was proximal to the OS on CT angiographic scans, revealed only a portion or nothing of their domes instead of their necks through the proximal dural rings after dissection of the distal dural rings. Dome coating with fibrin glue and a piece of muscle tissue or mere exploration was performed. Another aneurysm, of which the neck straddled the OS on CT angiographic scans, was found to arise across the proximal dural ring. Clipping of the neck was performed after dissection of the proximal dural ring. Of the source images of CT angiographic scans, the axial images were the most useful in evaluating the relationship of the neck of an aneurysm to the OS.

CONCLUSION: On CT angiographic scans, the OS is a precise identification of the proximal dural ring that forms the superior border of the cavernous sinus. The aneurysms whose necks arise obviously distal to the OS on CT angiographic scans are able to be clipped without dissection of the proximal dural ring.

KEY WORDS: Computed tomographic angiography, Optic strut, Paraclinoid aneurysm, Proximal dural ring

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Discriminating between intradural and extradural/intracavernous aneurysms of the internal carotid artery (ICA) is critical when considering treatment options. It remains difficult to make this distinction, however, because of the lack of reliable landmarks in image examinations (8). We focused our attention on the optic strut (OS), which is the small (3–5 mm) and obliquely oriented osseous bridge superiorly connecting the anterior clinoid process and medially connecting the sphenoid bone. The OS is an attachment site for the proximal dural ring (i.e., the anterior part of the proximal ring attaches to the inferior surface of the OS). The inferior border of the paraclinoid region is formed by the proximal dural ring, which is the anterior roof of the cavernous sinus (17, 18). Gonzalez et al. (4) considered the OS to be a candidate for the identification of the proximal dural ring during computed tomographic (CT) angiographic scans. This small osseous bridge is also visible or easily detectable in axial and coronal source images of CT angiographic scans. We demonstrate here the accuracy of the OS as a landmark for image examination during preoperative evaluation of a paraclinoid aneurysm.

PATIENTS AND METHODS

Between 1998 and 2005, 55 patients with 58 paraclinoid aneurysms were admitted to our hospital. Eight of these patients who were observed, but did not undergo surgery, were excluded from our study. Six patients with ruptured aneurysms were also excluded because it would have been inappropriate to examine the precise relationship of their necks to the proximal dural rings during surgery. The remaining 44 unruptured paraclinoid aneurysms in 41 patients were treated by direct surgery or endovascular treatment (EVT) (*Table 1*). Of the 21 lesions treated by direct surgery, 20 underwent the ipsilateral pterional approach and one underwent the contralateral pterional approach. In all surgical cases, the carotid bifurcation was exposed at the neck, the anterior clinoid process was drilled out, and the distal dural ring was dissected. Twenty-three lesions received either EVT only or extracranial-intracranial bypass followed by EVT. The method of treatment was chosen by each surgeon based primarily on the findings of digital subtraction angiographic scans. The lesions treated by direct surgery were categorized into four groups, including two subgroups according to al-Rodhan et al.'s (1) classification: one anterior wall lesion (Group Ia), four ventral paraclinoid lesions (Group Ib), nine true ophthalmic artery lesions (Group II), three carotid cave lesions (Group III), three transitional lesions (Group IV), and one cavernous lesion (Group V) (*Table 1*). Three lesions lacking preoperative CT angiographic scans were not included in our study. Eighteen lesions in 17 consecutive patients who underwent preoperative high-resolution CT angiographic scans and direct surgery were retrospectively evaluated using CT angiographic scans (i.e., using the axial, coronal, and sagittal source images) (*Table 2*). We focused on the relationship of the necks of aneurysms to the OS in CT angiographic scans and that of the necks to the proximal dural rings in the intraoperative findings. A neurosurgeon and a neuroradiologist blinded to the intraoperative findings identified the neck of aneurysms and the OS and judged the relationship between the location of the aneurysmal neck and that of the OS (i.e., whether the aneurysm is located distally or proximally to the OS) on the basis of CT angiographic scans.

TABLE 1. Number of aneurysms in each group of al-Rodhan classification

al-Rodhan's classification	Surgical group	Endovascular group
Ia	1	2
Ib	4	1
II	9	8
III	3	7
IV	3	0
V	1	5
Total	21	23

CT angiographic scans were performed on an eight-detector-row multidetector helical scanner (Aquilion, Toshiba Medical Systems, Tokyo, Japan). CT scans were obtained using 1.0-mm section collimation during a bolus intravenous injection of 50 ml of contrast medium. Multiplanar reformats were created using a 1.0-mm section thickness in the axial, coronal, and sagittal planes. We selected images that best profiled the OS and its relationship to the necks of paraclinoid aneurysms. Evaluations by CT angiographic scans were compared with the intraoperative findings.

TABLE 2. Summary of 21 patients in the surgical group[a]

Patient no.	Age (yr)/sex	Side	Group	Operating method	Site of neck to optic strut
1	38/F	L	Ia	Neck clipping	Distal
2	56/F	R	Ib	Neck clipping	X[c]
3	57/F	R	Ib	Neck clipping	Distal
4	55/F	L	Ib	Neck clipping	Distal
5	61/F	R	Ib	Neck clipping	Distal
6	69/F	L	II	RA + trapping (calcification)[b]	Distal
7	54/F	L	II	Neck clipping	Distal
8	68/F	L	II	Neck clipping	Distal
9	66/F	R	II	Neck clipping	X[c]
10	56/F	R	II	Neck clipping	Distal
11	19/M	L	II	Neck clipping	Distal
12	22/F	L	II	Neck clipping	Distal
13	50/F	L	II	Neck clipping	Distal
14	59/F	R	II	Neck clipping	Distal
15	41/M	R	III	Neck clipping	Distal
16	54/F	R	III	Neck clipping	Distal
17	61/F	L	III	Neck clipping	Both
18	69/F	R	IV	Coating only	Proximal
19	59/F	R	IV	Coating only	Proximal
20	64/F	R	IV	Exploration only	X[c]
21	69/M	L	V	Exploration only	Proximal

[a] L, left; R, right; RA, radial artery graft.
[b] Impossible to clip because of neck calcification.
[c] Patients who did not undergo preoperative computed tomographic angiography.

RESULTS

Between 1998 and 2005, 17 consecutive patients with 18 unruptured paraclinoid aneurysms (three men; 14 women; mean age, 54.7 yr; age range, 19–69 yr) who underwent preoperative CT angiographic scans and subsequent direct surgery were evaluated in regard to their CT angiographic scanning data and operative findings. During surgery, 14 out of 18 lesions distal to the OS in CT angiographic scans were found arising distal to the proximal dural ring. All lesions were clipped, except one exhibiting neck calcification. It was impossible to clip the lesion with neck calcification, so we performed an extracranial-intracranial bypass with a radial artery graft and trapping of the ICA. In Patient 10 (*Table* 2), the aneurysm was clearly distal to the OS in the axial and coronal source images by CT angiographic scans (*Fig. 1*, Group II). During surgery, the neck and the dome were found distal to the proximal dural ring, and the neck was clipped. In Patient 18, the neck was proximal to the OS, and only part of the dome (instead of the neck) was visible distal to the proximal dural ring (*Fig. 2*, Group IV). Dome coating was performed with fibrin glue and a section of muscle. In Patient 17, the neck straddled the OS from proximal to distal on CT angiographic scans, and direct surgery demonstrated that a portion of the neck was proximal to the proximal dural ring (*Fig. 3*, Group III). The proximal end of the neck was not visible even after the optic nerve was mobilized by canal unroofing and the distal dural ring was dissected, whereas the majority of the neck was distal to the proximal ring. Premature rupture occurred when neck clipping was attempted without sufficient dissection of the proximal dural ring. Finally, neck clipping was performed after sufficient dissection of the proximal dural ring, division of the ipsilateral ophthalmic artery, retrograde suction decompression (2), and exposure of the proximal end of the neck.

The coronal and axial source images of CT angiographic scans demonstrated in exquisite detail the necks of the paraclinoid aneurysms and the OS, whereas the sagittal source images often failed to demonstrate these features. The axial images, especially, precisely showed the relationship of the paraclinoid aneurysm necks to the OS.

DISCUSSION

It is extremely important to identify the locations of dural rings by radiographic examination because, if aneurysms in

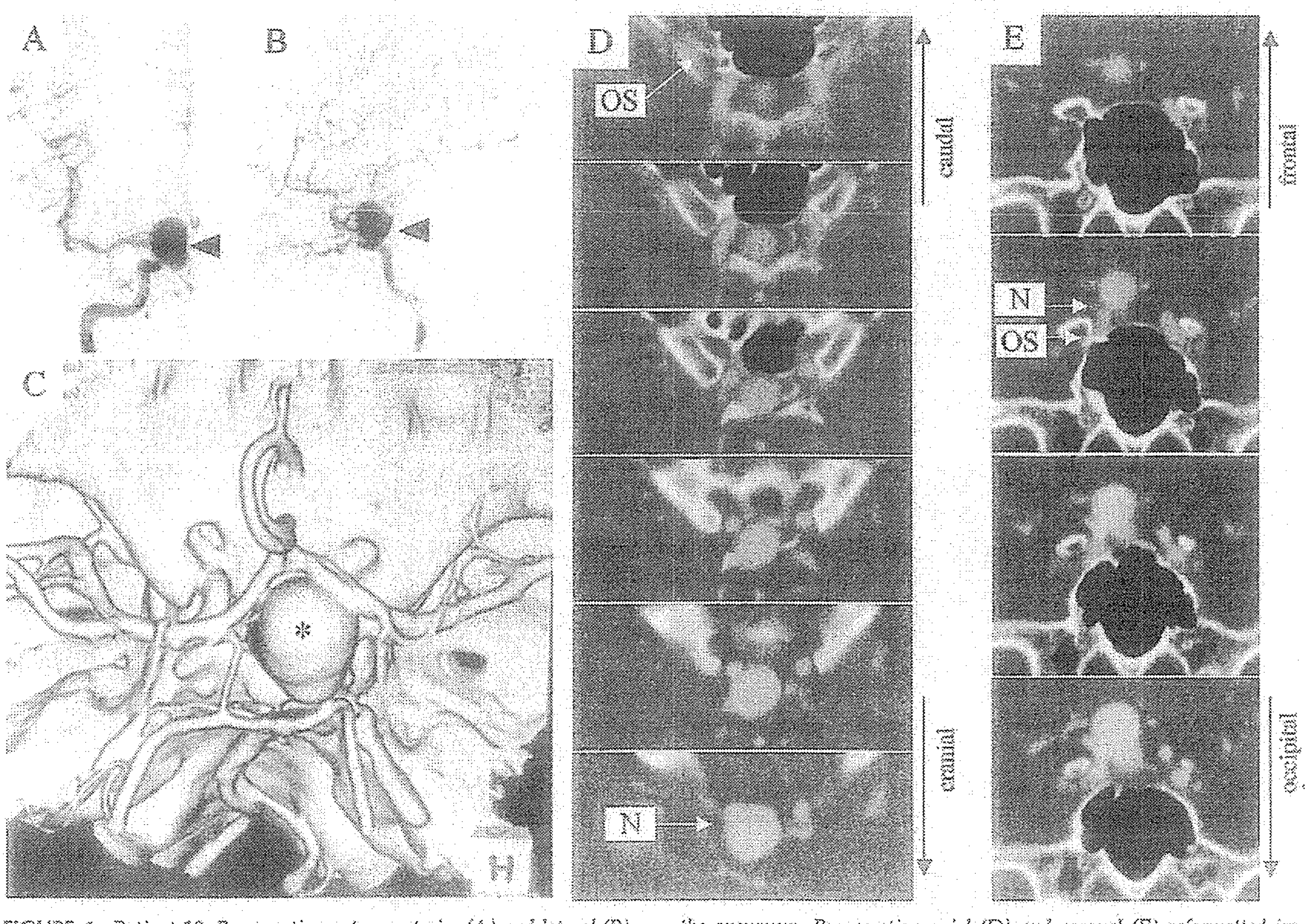

FIGURE 1. *Patient 10. Preoperative anteroposterior* (A) *and lateral* (B) *digital subtraction angiographic scans showing IC-ophthalmic aneurysm* (arrowheads) *(al-Rodhan Group II).* C, *preoperative three-dimensional reformatted CT angiographic scanning study, with an* asterisk *denoting the aneurysm. Preoperative axial* (D) *and coronal* (E) *reformatted images. Aneurysm arises distal to the OS.* Upper images *in* D *are more caudal, and* upper images *in* E *are more frontal. This aneurysm was clipped.* N, *neck of aneurysm.*

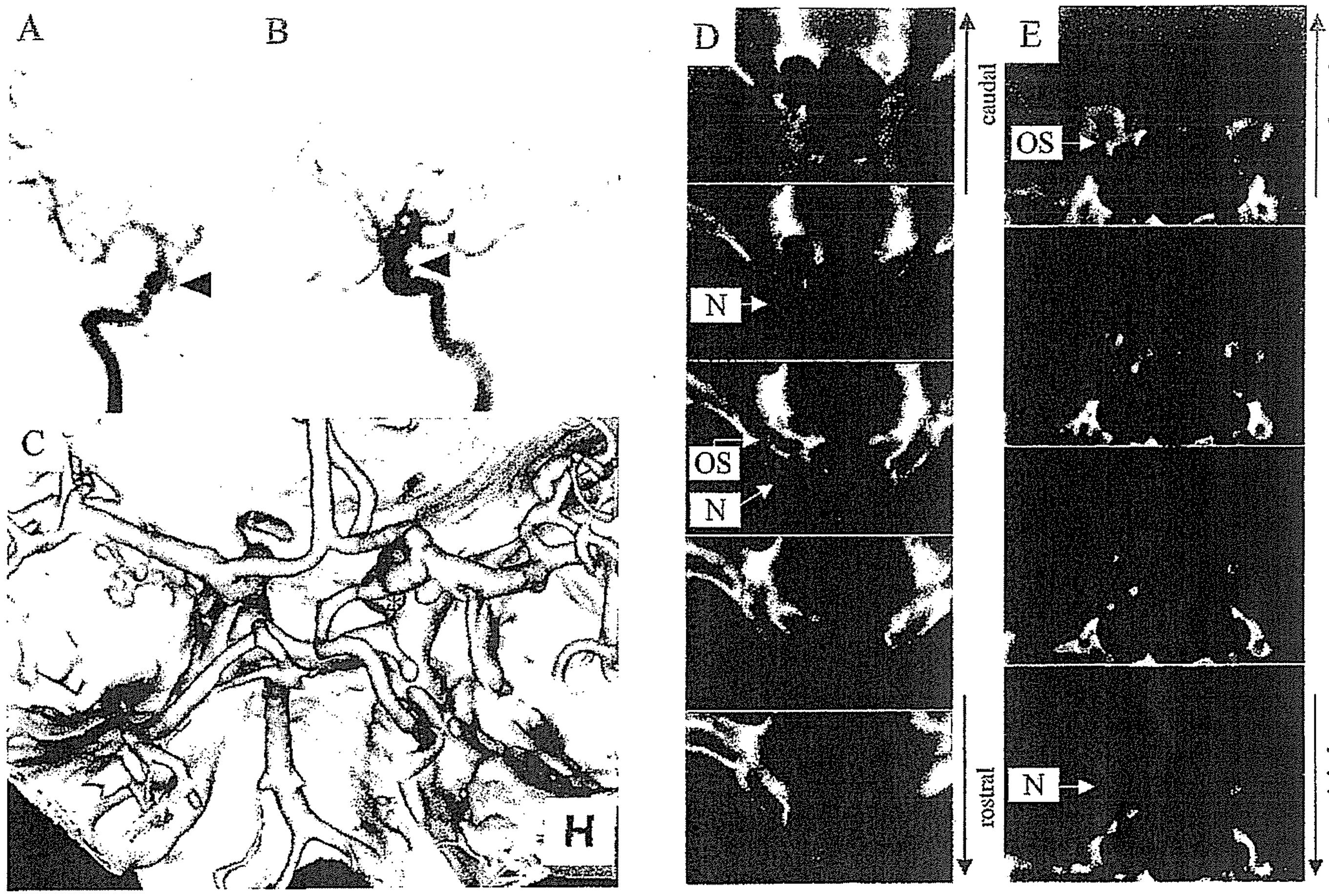

FIGURE 2. *Patient 18. Preoperative anteroposterior* (A) *and lateral* (B) *digital subtraction angiographic scans showing a small aneurysm* (arrowheads) *projecting medially (al-Rodhan Group IV).* C, *preoperative three-dimensional reformatted CT angiographic scanning study, with an* asterisk *denoting the aneurysm. Preoperative axial* (D) *and coronal* (E) *reformatted images. Axial images demonstrate aneurysm arising proximal to the OS. In coronal images, it is difficult to evaluate relationship of neck to OS. This aneurysm underwent dome coating with fibrin glue and a piece of muscle tissue because neck was in cavernous sinus.* N, *neck of aneurysm.*

the clinoid portion of the ICA are below the proximal dural rings, they are within the confines of the cavernous sinus and should be treated under the limited circumstances. However, it is often difficult to discriminate between intradural and extradural/intracavernous aneurysms of the ICA by digital subtraction angiography or magnetic resonance imaging scans. This problem is unresolved because of anatomic complexity in this region and the lack of reliable radiographic landmarks. Punt (16) proposed the ophthalmic artery to be a radiographic landmark, whereas Taptas (19) suggested that the anterior clinoid process could play a similar role. The origin of the ophthalmic artery is quite variable, although it typically originates from the dorsal surface of the ICA adjacent to the distal dural ring (5, 10, 11). The anterior clinoid process is also quite variable in size and shape (3, 6) and, therefore, cannot be a reliable landmark by which to discriminate paraclinoid aneurysms. Oikawa et al. (15) considered the most distal point of the distal dural ring to be the superior border of the anterior clinoid process and the proximal marker of the distal dural ring to be the tuberculum sellae. Murayama et al. (12) insisted that the concavity in the paraclinoid segment of the ICA was visible coincident with the attachment of the distal dural ring by CT angiography scanning. However, the condition of the vessel's surface could be affected by both atherosclerosis and calcification. As Gonzalez et al. (4) suggested, the OS might serve as a reliable radiographic landmark because it is a small osseous bridge that exactly defines the location of the proximal dural ring and is visible by CT angiographic scans. They analyzed five cadaveric heads and four patients. We further confirmed the accuracy and reliability of the OS as a landmark in CT angiographic scans by analyzing in 17 consecutive patients (18 aneurysms). The location of paraclinoid aneurysms could be estimated in CT angiographic scans with reference to the OS. This radiological evaluation is quite useful in selecting treatment modalities or even choosing treatment or observation.

In the present study, the axial source image of CT angiographic scans most precisely demonstrated the relationship of

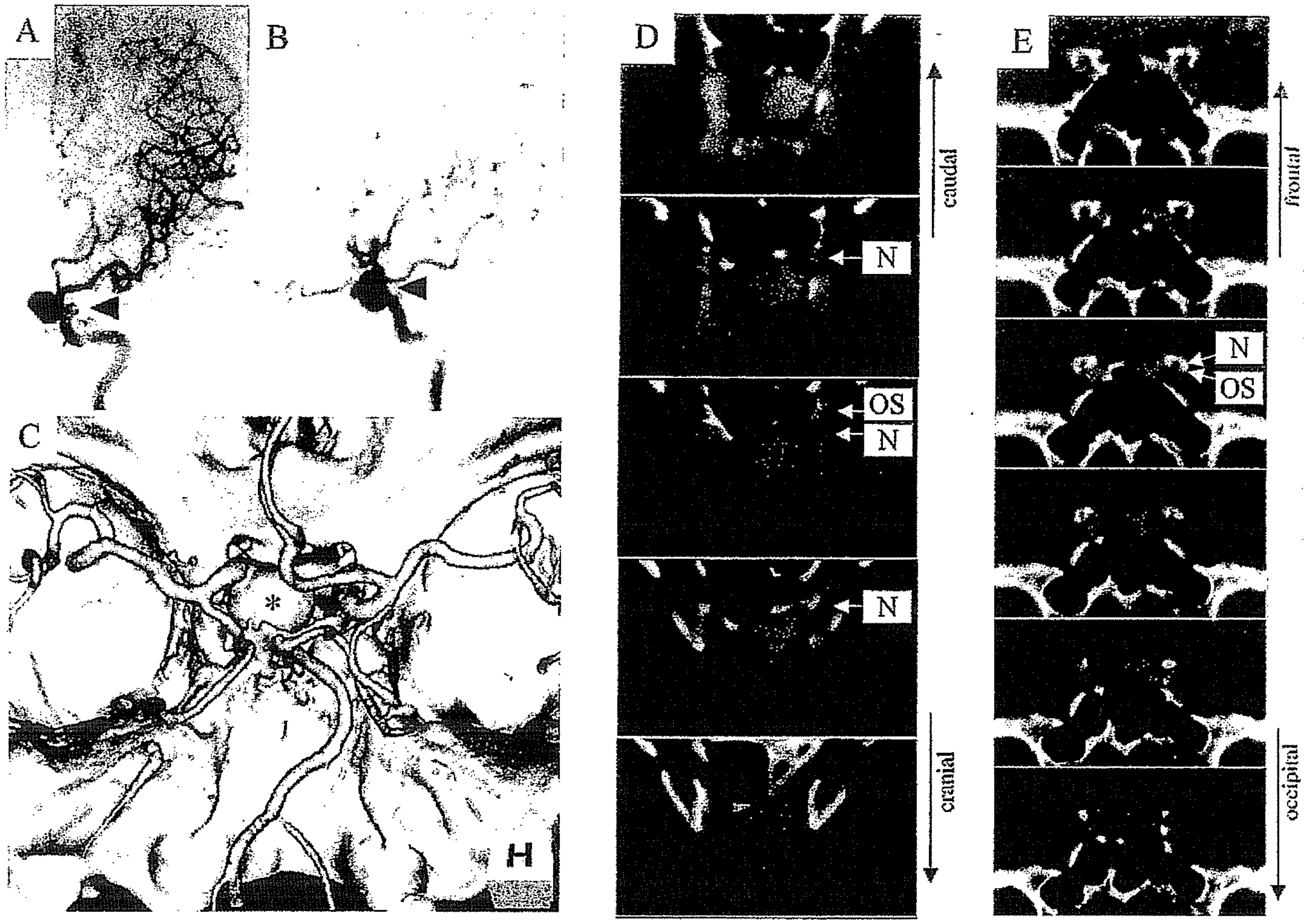

FIGURE 3. *Patient 17. Preoperative anteroposterior (A) and lateral (B) digital subtraction angiographic scans showing an aneurysm (arrowheads) that involves the clinoid portion and projects medially (al-Rodhan Group III). C, preoperative three-dimensional reformatted CT angiographic scanning study, with an* asterisk *denoting the aneurysm. Preoperative axial (D) and coronal (E) reformatted images. The neck of the aneurysm straddles the OS. This aneurysm ruptured prematurely and was finally clipped after dissection of the proximal dural ring.*

the neck to the ICA and the OS. The clinoid portion of the ICA is nearly vertical to the plane of the axial image. The directions in which aneurysms project from the clinoid portion is nearly parallel to the plane of the axial image. Thus, the axial images seem to be the most appropriate for the detection of the neck projecting in any direction. Nagasawa et al. (13) advocated the axial source images of magnetic resonance angiographic scans as useful for the evaluation of paraclinoid aneurysms. CT angiographic scans can reveal the osseous structures in finer detail. In the coronal source images, the OS was more easily detected, but the neck was sometimes unclear. It was also often difficult to understand the relationship of the neck to the OS in the sagittal images.

According to our analysis, aneurysms proximal to the OS should be within the confines of the cavernous sinus. More accurately, however, the aneurysms with necks that are entirely proximal to the proximal dural ring (i.e., the OS in CT angiographic scans) may grow, and their domes can protrude into the subarachnoid space (al-Rodhan Type IV) or the space between the rings. Relatively large aneurysms projecting superiorly should be carefully estimated in regard to the relationships of both their domes and necks to the OS. It is of primary importance to recognize that aneurysms located between the two dural rings (i.e., interdural-ring aneurysms) can also cause subarachnoid hemorrhage (14). Therefore, it is clinically ideal for the relationship of the neck/dome to the proximal dural ring, not the distal ring, to be analyzed correctly.

In the case of aneurysms with necks that are broad and close to the proximal dural ring, the most important feature is the proximal end of the neck. If the proximal end of the neck is proximal to the proximal dural ring, neck clipping requires dissection of the proximal dural ring, which will cause intrusive venous bleeding from the cavernous sinus. In Patient 17, we were able to hold the distal end of the neck with little trouble, but we found it difficult to hold the proximal end of the neck; even the proximal dural ring was dissected. Therefore, very precise preoperative evaluations are needed. It would be helpful to examine in detail the relationship of the proximal end of the neck to the OS. EVT might have been the first choice for Patient 17 if the relationship of the neck to the proximal dural ring was understood preoperatively in better detail (7).

In devising strategies for the treatment of aneurysms in this region, the location of the neck or dome is not the only concern. Generally, a superolaterally projecting aneurysm expands into the anterior clinoid process, making the operative procedure extremely hazardous (9). It is not easy to drill an anterior clinoid process into which an aneurysm is expanding or to execute an optimal microsurgical procedure without intrusive bleeding from the cavernous sinus. Obviously, proximal control of the ICA is critical during surgery for paraclinoid aneurysms. With this in mind, a preoperative balloon test occlusion of the ICA is advisable. Moreover, excellent anatomic knowledge and preoperative evaluations are essential. Surgical treatment is not the only option; when uncertain, EVT, including carotid sacrifice with bypass, may be an alternative method.

During the surgery, we attempted to identify the anatomic structure in this area as close as possible, if the information was necessary. In some cases, we could confirm that the roof of the cavernous sinus (i.e., the proximal dural ring) was attached to the inferior surface of the OS. In the other patients, however, bleeding from the cavernous sinus prevented our precise observation. A notch that was occasionally identified in the clinoidal portion of the ICA coincided with the attachment of the distal dural ring and was distal to the OS in all the available cases.

The case series in this study contains consecutive patients who underwent preoperative CT angiographic scans and direct surgery. Accordingly, most of these cases are intradural. A randomized, double-blind study would ideally confirm the accuracy of the OS as a landmark for the proximal dural ring. However, it is extremely difficult (and even unethical) to undertake these studies because an aneurysm appearing to be obviously intracavernous would be treated endovascularly or usually observed. Methods of confirmation might be confined to retrospective studies or to case studies of multiple aneurysms that are intradural and intracavernous in the same side. We think the objectivity of this study was ensured because the cases were consecutive, although the number of the patients was small, and there is a lack of balance of cases with aneurysms proximal to the OS in CT angiographic scans.

CONCLUSION

Discrimination between intradural and extradural/intracavernous aneurysms is indispensable for the selection of treatment options and surgical planning. It is difficult to preoperatively clarify the relationship of paraclinoid aneurysms to the distal/proximal dural ring because of the anatomic complexity in this region. Three-dimensional CT angiographic scanning was performed, and the source images were retrospectively analyzed, to evaluate in detail unruptured paraclinoid aneurysms of the ICA. CT angiographic scans demonstrated accurate interrelationships between the ICA, domes and necks of aneurysms, and neighboring osseous structures. We demonstrated that three-dimensional CT angiographic scanning is capable of confirming whether a paraclinoid aneurysm is intradural or extradural/intracavernous on the basis of the OS. Preoperative radiographic examination with this technique would be useful in selecting appropriate management of cases and maximizing the safety of surgical procedures, such as clipping unruptured aneurysms of the paraclinoid segment of the ICA.

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COMMENTS

The authors have demonstrated the relationship between the optic strut and the proximal dural ring on computed tomographic angiography (CTA). They have retrospectively reviewed a small series of patients undergoing surgery for proximal carotid aneurysms to determine if that relationship can be used to predict whether or not an aneurysm is intracavernous, arising on the clinoidal segment of the carotid, or within the subarachnoid space.

This distinction is of more than just academic interest. Aneurysms arising wholly within the cavernous sinus are associated with a much more benign natural history and extremely low risk of subsequent subarachnoid hemorrhage (SAH). Those aneurysms arising on the clinoidal segment of the carotid between the two dural rings are partially protected from SAH because of the surrounding bone and dura. However, if they enlarge they may pierce the dural ring and present into the subarachnoid space and are thus intermediate in terms of risk. Those aneurysms that are above the dural ring lie completely within the subarachnoid space and would thus carry a greater risk of SAH.

Traditionally, it has been difficult to accurately predict where the neck of a proximal internal carotid artery aneurysm arises. Variability in the location of the ophthalmic artery and variation in size of the anterior clinoid process make these anatomic structures unreliable.

Although this is a small series, the authors have demonstrated that the relationship between the optic strut, which is readily seen on CTA, and the proximal dural ring may be reliable enough to assist in clinical decision-making.

Daniel L. Barrow
Atlanta, Georgia

In this report, the relationship between the optic strut and the necks of paraclinoid aneurysms was analyzed using CTA to determine whether or not an aneurysm was located distal to the proximal dural ring and, therefore, beyond the cavernous sinus. This knowledge is important because it identifies those aneurysms that can bleed into the subarachnoid space and those that can be microsurgically clipped. Aneurysms, located proximal to the proximal dural ring are in the cavernous sinus, are not considered at risk for SAH, and are typically managed conservatively. The dural rings are soft tissue structures that cannot be imaged directly. However, Gonzalez et al. (1) demonstrated that the optic strut is a surrogate marker of the proximal dural ring and that it can be imaged with CTA. Hashimoto et al. applied this CTA analysis to a clinical series of 17 patients with 18 aneurysms and observed good correlation between the images and the intraoperative findings. Therefore, CTA can be used to identify paraclinoidal aneurysms that might cause SAH and to select patients for microsurgical management.

Whereas computed tomographic imaging is useful for these purposes, it should also be used to identify aneurysms not suited for surgery. Calcified aneurysms and aneurysms in front of the proximal dural ring are better managed with endovascular techniques because of the difficulties in applying the clips to a calcified neck and visualizing the proximal neck of an intracavernous aneurysm. There were four of these aneurysms in this report, and the authors struggled with some of these aneurysms. In my practice, paraclinoidal aneurysms that are not clearly in the subarachnoid space, beyond the proximal dural ring, are either observed if asymptomatic or referred for coiling because the endovascular results are excellent and the risks are substantially less. Therefore, CTA is becoming an important tool for selecting surgical patients and optimizing microsurgical results. We are indebted to the neurosurgical anatomists who clarified important relationships between the optic strut, the dural rings, and paraclinoidal aneurysms because the technique described in this report is simply an application of this critical knowledge.

Michael T. Lawton
San Francisco, California

1. Gonzalez LF, Walker MT, Zabramski JM, Partovi S, Wallace RC, Spetzler RF: Distinction between paraclinoid and cavernous sinus aneurysms with computed tomographic angiography. Neurosurgery 52:1131–1137, 2003.

The authors have reviewed a consecutive series of patients treated surgically for paraclinoidal carotid aneurysms who received preoperative CTA. This series is important because each case described was actually clarified with intraoperative exposure. The authors found that when the necks were distal to the optic strut by the axial CTA cut, the actual aneurysm was distal to the proximal dural ring. This finding is particularly important in managing the increasing population of patients discovered incidentally to harbor paraclinoidal carotid aneurysms. The question of whether or not the neck (and fundus) is within the subarachnoid space is critical to determine whether or not any treatment should be considered. The problem with using a simple landmark, such as the optic strut, relates to the complexity of the anatomy as the carotid emerges from the cavernous sinus. The dural ring is oblique to the axial, coronal, and sagittal planes. To make matters worse, the particular orientation of the ring is quite variable. The ultimate resolution of this important question will require merging of multiple imaging modalities in three dimensions to be able to identify bone, vessel wall, lumen, and dura to perfectly represent the patient's unique anatomy.

H. Hunt Batjer
Chicago, Illinois

Surgical treatment of paraclinoid aneurysms is frequently complicated by the relationship of the neck of the aneurysm to the cavernous sinus. When the neck partially or completely exists proximal to the proximal dural ring, clipping is extremely difficult. In these cases, the cavernous sinus usually has to be opened substantially and packed to control venous bleeding. Given my own experience with cavernous sinus surgery, I prefer to have these types of aneurysms treated endovascularly or, when unruptured, with observation only. In this study, Hashimoto et al. have demonstrated fairly convincing evidence that preoperative evaluation of CTA data can adequately predict the relationship of the aneurysm neck to the proximal dural ring. The optic strut is a discreet bony landmark that forms an anchor for the proximal ring and, therefore, can be useful to localize the neck of the aneurysm to the cavernous sinus. The observations in this study confirm previous predictions that the optic strut may be the most useful landmark for preoperative planning.

Robert A. Solomon
New York, New York

The investigators performed a retrospective analysis of 17 consecutive patients with 18 aneurysms who underwent preoperative CTA. In their evaluation, they focused on the relationship of the neck of the aneurysm to the optic strut on the CTA. Direct surgery in that group revealed that 14 of the aneurysms in which the necks were distal to the optic strut by CTA arose distal to the dural ring, enabling all the lesions to be treated by clip ligation with the exception of one that had a calcification. There are certain situations in which the exact location of the neck in relation to the dural ring cannot be ascertained, and I find this to be a useful adjunct. Since reviewing this report, I have been looking at this prospectively in our own patient populations and have found it to be useful. When considering endosaccular occlusion this is not important. However, in planning a preoperative surgical exposure it becomes extremely critical and I think it is a very useful tool.

Robert H. Rosenwasser
Philadelphia, Pennsylvania

The Extraction of the Stone of Folly *(top) (oil on panel, mid-16th century) after Hieronymus Bosch (courtesy of Bailliad, Musée Benoit de Puydt).*

Operation for Stone *(bottom) (oil on panel, 1550–1575; follower of Hieronymus Bosch (P. Gracziel 1556) (courtesy of Saint-Omer, Musée de l'Hôtel Sandelin).*

3 未破裂脳動脈瘤

秋山幸功　寳金清博

未破裂脳動脈瘤は，大きく分けて無症候性および症候性に大別できる．前者は主に脳ドックや，脳梗塞など他の脳疾患の精査などによって発見されることが多い．後者は動脈瘤が周辺の脳または脳神経などを圧迫することにより脳神経麻痺など何らかの神経症状を出すものである．普通サイズが増大傾向にあるものに多く，そのため破裂の危険性が高いと考えられる．

世界的には未破裂脳動脈瘤の年間破裂率は1〜2%とされ[1]，わが国では，Yasuiらが年間破裂率2.3%と報告している[2]．また，国際共同研究（ISUIA）では10 mm以下の動脈瘤の年間破裂率は0.05%，10 mm以上では年間1%，25 mm以上では最初の1年で6%と報告され[3]，この報告に対しては，対象脳動脈瘤のサイズに偏りが強く異論が多く出されている．脳動脈瘤の正確な破裂率を算出するには，たとえばrandomized studyのようにバイアスがかかっていない多数の治療例および非治療例を前向きに追跡調査する必要がある．しかし現実的には不可能であり，疫学的な調査から概算を出すほかない．現在，わが国で行われている日本未破裂脳動脈瘤調査（Unruptured Cerebral Aneurysm Study of Japan：UCAS Japan）において2004年1月現在で，6,017例7,386動脈瘤の調査結果が発表され，0.64%／年の破裂率とされる．これら未破裂脳動脈瘤の有病率，破裂の危険性，および治療による合併症などを総合的に検討し未破裂脳動脈瘤に対する治療が決定されるべきであろう．

診断と検査

1．症状と臨床所見

症候性未破裂脳動脈瘤の症状で代表的なものは動顔神経麻痺である．脳動脈瘤による機械的圧迫が原因であり，ふつう内頸動脈-後交通動脈瘤や，脳底動脈-上小脳動脈瘤などが動眼神経を直接圧迫することによる．動脈瘤のサイズが大きいもの，また拡大傾向にあるものに多いとされ，破裂の危険性が高いと考えられている．

2．画像診断

a）脳血管撮影：以下に述べる3D-CT angiographyやMRAなど，より侵襲の少ない検査が注目されている中，現在でもなお，脳動脈瘤の検出，動脈瘤周囲の状況の把握など，血管撮影の利用価値は高い．また，現在では3D-CT angiographyなどの開発により低侵襲化され，立体構造の把握なども容易になってきている．

b）3D-CT angiography：動脈瘤の検出率に関して血管撮影よりは劣っており，血管撮影の85〜98%の検出率と報告[4]されているものの，動脈瘤周囲の血管や骨との関係など，治療に際して必要な情報を3次元で観察することができる点で優れている．また，血管撮影と比較して，より低侵襲で，かつ短時間で行える検査方法であり，現在では，血管撮影をせず，3D-CT angiographyのみで治療に移る施設も多くなってきている．

c）MRA：最近，MRI，MRAが無侵襲であることから脳血管障害に対し汎用される検査となってきている．そのため，偶発的に動脈瘤が発見される機会が増えてきている．

治療の一般方針

1．治療方針の立て方

未破裂動脈瘤の治療の適応は，破裂の危険性と治療による合併症の危険性の引き算で決められる．統計学的な脳動脈瘤の破裂の危険因子は，動脈瘤の背景にばらつきが多いためさまざまであるが，家族歴，性別，喫煙，大きさ，多発性，高血圧，高脂血症，糖尿病などがあげられ，そのうち喫煙を続けている場合は3.04（p＝0.02）に上昇するといわれている．家族歴では，一親等以内の動脈瘤患者が2人以上いる場合には，一般の4.2倍，1人では1.8倍の未破裂脳動脈瘤の発見率に．また，二親等以内のくも膜下出血の家族歴をもつ者では，スクリーニングを受けた患者の14%に未

破裂脳動脈瘤が発見されたと報告されている．破裂の危険因子を検討し，破裂の危険性が高いと判断されたものは，積極的な治療が勧められる．

手術における合併症については，King らのメタ解析では手術死亡は 1%，合併症は 4%と報告されている[5]．施設や術者の経験によっても手術成績は大きく異なり，Solomon らは，年間 10 例以上の未破裂脳動脈瘤を開頭手術する施設では合併症出現率が 5.3%であったのに対し，10 例未満の施設では 11.2%にも達していたと報告している．

治療の適応は症例ごとに検討すべきであるものの，ある程度の標準的な治療ガイドラインを決めておく必要がある．Zuccarello は，手術適応として，①全身状態のよいすべての症候性脳動脈瘤，②すべての巨大動脈瘤，③全身状態の良好な 45 歳未満のすべての無症候性脳動脈瘤，④全身状態の良好な 45～65 歳の 10 mm を超えるすべての無症候性脳動脈瘤，の 4 つをあげている．また，American Heart Association（AHA）のガイドライン[6]において，1998 年の共同研究の結果をふまえて，①海綿静脈洞内の内頸動脈瘤では小さなものは治療の必要はなく，大きな症候性のものは個々に検討，高齢者ではとくにリスクを考慮する．②症候性脳動脈瘤は大きさにかかわらず治療対象となる．③別の脳動脈瘤の破裂によるくも膜下出血の既往がある場合は治療対象となる．④くも膜下出血の既往のない 10 mm 未満の無症候性脳動脈瘤は経過観察するが，年齢が若い場合，動脈瘤に daughter sac がある場合，家族歴がある場合，経過観察中に増大がみられる場合などは治療を考慮する．⑤ 10 mm 以上の無症候性脳動脈瘤は治療対象となる．

わが国では 1997 年，脳ドック学会において無症候性未破裂脳動脈瘤の手術適応に関して次のようなガイドラインをあげている．①脳動脈瘤が硬膜内にある，②大きさが 5 mm 前後より大きい，③年齢が 70 歳以下，なお，手術治療がなされない場合は，1 年以内に経過観察を行い，増大を認めた場合は手術を勧める．

2. 薬物療法

未破裂脳動脈瘤に対して薬物療法のみで根治することは不可能である．しかし未破裂脳動脈瘤に対する保存療法においては，薬物を用いた血圧の安定化が重要となる．

3. 外科的治療法

a）動脈瘤頸部クリッピング術：クリップの種類に関して，現在はチタン性クリップが汎用されている．把持力が比較的弱いとされるものの，術後の MRI などによる画像によるフォローにおいてアーチファクトが少ないことなど利点が多い．

b）動脈瘤のラッピングまたはコーティング：ゴアテックスなどによって動脈瘤を覆うことによって破裂の危険性を軽減させる治療法．クリッピング術の困難例に用いられる．

c）トラッピング術：外頸動脈系からのバイパス術を併用して，脳動脈瘤の親血管を閉塞してしまう治療法で，巨大脳動脈瘤などに対する治療で頻用される．

4. その他の治療法

未破裂脳動脈瘤に対する他の治療法としてコイル塞栓術を含む血管内手術があげられる．動脈瘤内に電気的離脱可能な platinum coil（Guglielmi detachable coil：GDC など）を動脈瘤内に留置することにより血栓化を促進しようとする治療法である．2002 年に ISAT のデータが発表され，その中でコイルによる塞栓術のほうが開頭術によるクリッピング術よりも短期予後がよいと報告された．後にこの報告に対し多くの反論が出ている．現在のところ長期フォローの成績は報告されておらず，また，術中術後の合併症も報告されている．とくにコイル塞栓術における動脈瘤穿孔の発生率は 1.3～5.8%と報告されている[7,8]．再治療を要した症例も少なくなく，その有用性については議論の余地があり，現段階では，開頭術を含めた根治術を基本におき，手術における高リスク群や，手術アプローチ困難例，手術を拒否される患者などに対して勧められるべき治療法と思われる．

患者指導のポイント

患者指導の中心は危険因子である喫煙，高血圧，高脂血症といった，患者自身でコントロール可能な，脳動脈瘤破裂危険因子をできる限り排除するよう指導することであろう．

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トピックス

u-CARE 研究

近い将来，オンサイト調査協力施設を中心に未破裂動脈瘤の治療方針のばらつき，および治療方針決定におけるバイアスについてインターネットを用いた情報交換を行って，SF-36v2.0 スタンダード版，SF-8，EQ5D 併合アンケート票などを用いて詳細な結果を調査することを目的とした臨床研究（u-CARE）が実施される予定である．

原著

日本未破裂脳動脈瘤悉皆調査（UCAS Japan）：中間報告III

UCAS Japan 事務局

Interim Report of the Unruptured Cerebral Aneurysm Study in Japan III

by

UCAS Japan Study Group

Unruptured cerebral aneurysm study in Japan (UCAS Japan) is conducted to clarify natural course and treatment risks of unruptured cerebral aneurysms (UCA), and build national data bank. This is a prospective cohort study and enrolled patients are cases with newly diagnosed UCA after Jan. 1. 2001. Data of all patients with UCA. either treated or observed, are stored into the head-quarter computer through internet registration. All cases are scheduled to have periodic follow-up at 3 months, 12 months and 36 months after diagnosis. As of April 2003. 4,940 patients (6.080 aneurysms) with newly diagnosed UCA were registered from 395 institutions. So far, there is a difference in registry status between geographic locations in Japan. Male-female ratio was 1 : 2 and median age of patients was 64 years old. Size of aneurysm ranged 3～45 mm (median 5 mm). The most frequent reason for imaging, which leaded diagnosis of UCA, was ill-defined symptoms such as headache or dizziness. Multiple aneurysms were found in 17% of cases and 96% of aneurysms were saccular ones. At the first registration, craniotomy was indicated in 34% and endovascular treatment in 5% of cases. Three months follow-up were reported in 4,077 cases and 12 months report in 2,285 cases. Treatment was performed in 1,743 cases with 2,007 aneurysms. So far. data of 4,090 person-year has been constructed. We are planning to call for further patient's enrollment and conform reliable data source to direct future management of UCA.

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Key words : unruptured cerebral aneurysm. prospective cohort. natural course, management risks. UCAS Japan

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はじめに

未破裂脳動脈瘤の治療方針を決定するためには，その自然歴および治療成績に関するエビデンスが必要である．これまで未破裂脳動脈瘤についてさまざまな検討がなされてきたが，その多くが後ろ向きのデータ解析であり，また治療結果の評価も一定の方法でなされていない[14]．そこでレベルの高いデータを構築するため前向きコホート研究が重要となる．最近国際未破裂脳動脈瘤研究（ISUIA）の前向きデータが報告されたが，1998 年に報告されたデータとはかなり自然歴に相違が認められる[6)7)]．本邦においては日本脳神経外科学会主導で 2001 年 1 月 1 日から未破裂脳動脈瘤の前向き悉皆調査が開始された[17]．本報告ではその調査の方法．これまでの登録状況・問題点および将来の計画について報告する．

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Table 1　UCAS Japan registered status as of April 4, 2003

Criteria	Description
Registered cases	4,940 patients, 6,080 aneurysms
Male：Female	1,678：3,262
Age	20-98 (median 64) years old
Multiple	866 cases (17%)
Family history	12%
Past history/social history	Hypertension 44%, Smoking 17%, Hyperlipidemia 14%, Cerebral ischemia 7%, Diabetes 6%, SAH 3.5%
Reason for imaging	Headache, dizziness 46%, CNS evaluation 27%, Brain doc 16%, SAH 5%, Symptomatic 4%, Others 2%
Neurological handicap at initial presentation	17%
Saccular aneurysm	96%
Bleb/Daughter sac	17%
Size of aneurysm	～4 mm：48%, 5, 6 mm：25%, 7, 8, 9 mm：15%, 10 mm～：12%
Location of aneurysms	MCA 34%, ICA 33%, Acom 14%, VB 9%
Follow-up	3 months：4,077 cases, 12 months：2,285 cases
Change	Total 189 cases, rupture 46 cases
Management	1,743 cases (2,077 aneurysms) Open 1,772, Endovascular 228, Both 7 aneurysms

CNS：Central nervous system, SAH：subarachnoid hemorrhage, MCA：middle cerebral artery, ICA：internal cerebral artery excluding cavernous IC, Acom：anterior communicating artery, VB：vertebrobasilar artery
(Data of Japan Neurosurgical Society)

対象と方法

本調査の現在に至る経緯，調査対象や方法の詳細については中間報告 I [16]，II [17] および本調査ホームページ (https://endai.umin.ac.jp/islet/ucasj/ および http://ucas-j.umin.ac.jp/) を参照していただきたい．

1 調査対象

調査対象施設は日本脳神経外科学会認定 A，C 項施設およびその関連施設，それ以外の未破裂脳動脈瘤を診療する医療機関である．各施設の倫理委員会またはそれに準ずる組織にて，本調査への参加が許可された施設とした．対象となる患者はこれらの医療機関において，2001 年以降新たに発見された未破裂脳動脈瘤症例である．動脈瘤の最大径は 3 mm 以上のものとし，患者年齢は 20 歳以上とした．調査参加への十分な説明を行い，インフォームド・コンセントを得た後，患者の登録を行うこととしている．

動脈瘤の診断基準は high speed helical CT にて得られた CT angiography (CTA)，0.5 tesla 以上の MRI 機種にて得られた MR angiography (MRA)，または通常の脳血管撮影 (digital subtraction angiography を含む) をもとに，脳神経外科専門医，神経内科専門医または放射線科専門医が診断したものであり，診断ガイドラインに準拠して診断また計測されたものであることとした．

2 調査方法

この調査はあるがままの未破裂脳動脈瘤の経過を，治療例，経過観察例をすべて順次前向きに調査するコホート調査であり，治療方針には制約を設けず，各施設の医師の判断および患者の選択に従うこととした．患者登録は 2001 年 1 月 1 日より全国にて開始し，2003 年 12 月末まで新規患者登録を行い，全症例を 3 年間以上経過観察する．経過観察の開始時期として各施設の担当科における動脈瘤を発見するきっかけとなった最初の診察日を Day 0 と定義した．経過観察登録として Day 0 から 3 カ月，12 カ月，36 カ月の時期になんらかの方法 (外来や電話連絡) にて患者の近況を調べ登録する．治療や患者の変化または画像撮影が，この各調査時期の間にあった場合には，それについて追加フォームを記載する．もし患者が死亡したり動脈瘤が破裂した場合は調査の終了となり，その時点で終了登録を行う．

初期登録内容としては患者施設内 ID，生年月日，イニシャル，性，動脈瘤発見のきっかけ，診断の基準検査，家族歴，既往歴，最大 5 個までの瘤の部位，サイズ，形状，初期登録時における治療方針など約 100 項目のデー

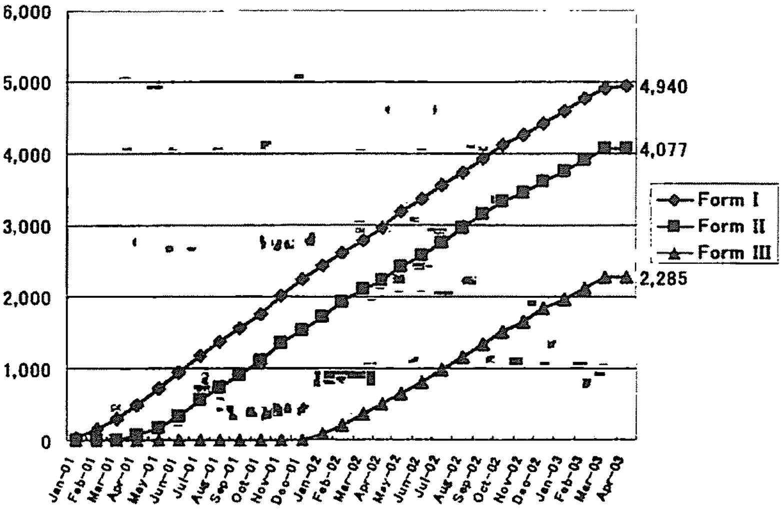

Fig. 1 Trends of UCAS Japan registry status
Form I：initial registration, Form II：follow-up registration at 3 months,
Form III：follow-up registration at 12 months.
150〜200 new cases were enrolled to this registry each months.

タを登録する．経過観察時においては，治療・変化や画像のない症例では観察日，神経症状など 20 項目程度，一方，治療・変化・画像のある症例では，治療された瘤の番号，治療の理由，治療後の症状・合併症，変化の種類，瘤の形状変化など最大 200 項目のデータをチェック方式で登録する．

患者の登録方法としてデータ処理を迅速化，簡便化するため，十分にプライバシー保護に配慮しながら，インターネットホームページにてデータを収集している．インターネット設備のない施設では，FAX または郵送によるデータの送信・入力を行う．またオンラインでの登録を行っていることを利用して，各患者の登録時期の接近や超過を知らせるため，またデータの入力確認のため，中央コンピューターから自動的に病院調査担当者に連絡が E-mail にて届くよう構築した．

本調査では来院治療または経過観察される患者全例の登録を目指しており，本事項の確認のため，毎年無作為に参加施設 10 施設を抽出し，実際の登録状況，患者のインフォームド・コンセント取得の有無，画像評価基準などを確認する．

結 果

2001 年 1 月 1 日より正式オンライン登録が開始されており，2003 年 4 月 3 日の時点でのデータを Table 1 にまとめる．登録施設は 395 施設（A 項施設 213，C 項施設 177，それ以外 5 施設）である．初期登録は 5,394 症例でなされたが，瘤のサイズが 3 mm 未満である例や，Day 0 が 2001 年以前である例など 454 例を除外し，4,940 例 6,080 個の瘤が今回の検討対象になった．診断基準として脳血管撮影が用いられたもの 2,145 例，MRA 2,444 例，CTA 1,244 例であった．

登録は 2001 年に登録を開始して以来順調に増加し，月 150〜200 例のペースで増加している（Fig. 1）．地域別の登録状況は北海道・東北地域で人口当たりの登録者が多く，九州・沖縄地区と関東地方で登録数が人口比では少ない（Fig. 2）．

患者の内訳は男性 1,678 例，女性 3,262 例と女性は男性の約 2 倍であった．年齢は 20〜98 歳（中間 64 歳）で，家族歴は 12%の症例で認められた．瘤を発見するきっかけとなった経緯は頭痛，めまいなどの不定愁訴についての精査で発見されたものが 46%で最も多く，次いで脳梗塞や中枢神経系疾患の精査の一環としての画像で発見されたもの 27%，脳ドック 16%，クモ膜下出血の検査で発見されたもの 5%，症候性 4%，その他 2%であった．瘤の部位は中大脳動脈 34%，内頸動脈 33%，前交通動脈 14%，椎骨脳底動脈 9%の順で多く，通常破裂例で 30〜40%を占める前交通動脈瘤は比較的少ない．大きさは 4 mm 以下のものが多く 48%，5 mm・6 mm 25%，7〜9 mm 15%，10 mm 以上 12%であった．

患者初期登録時の治療予定は，開頭手術が 34%，血管内治療が 5%の症例に適応されている．これらは患者の年齢（高齢者 75 歳以上では治療適応となる例が少ない）および瘤の大きさ（4 mm 以下の小型の瘤では治療適応

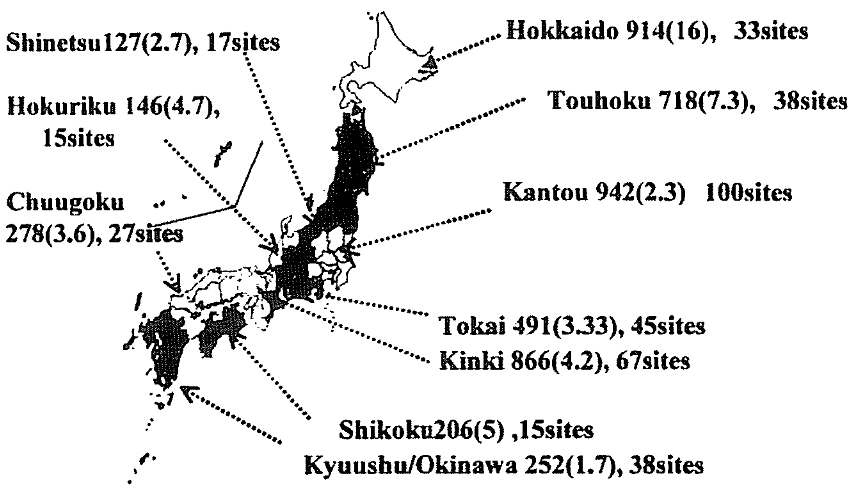

Fig. 2　Geographic distribution of registered cases

となるものが少ない）にて有意に影響された．

経過観察のうち3カ月後経過は4,077例，12カ月後経過は2,285例で登録されており，変化が77例，追加画像撮影が2,302例報告されている．変化のうち破裂は9例であった．緊急（FORM E）登録による調査の終了は112例にてなされ，終了の理由は破裂37例，瘤破裂以外の患者死亡は38例，その他37例（他院への転院など）であった．総計46例が破裂しているが，破裂例のなかには事後登録もあり，破裂率の測定には1例ごとの詳細な検討が必要である．本調査はあくまで中間報告であるので詳細な破裂率の報告はできないが，純粋な経過観察中の破裂例の報告が認められており，総症例の破裂率は0.5%/年を超える見込みである．破裂率に関与し得る因子として瘤の大きさ（1 cm以上のもの），部位（脳底動脈瘤），年齢（高齢者），性（女性）等が破裂率を増大させる因子である可能性がある．

一方，治療は1,743例2,007瘤に施行され，手術が1,772個の瘤に，血管内治療が228個の瘤に，両方が7個の瘤に施行された．治療の理由として患者の希望が70%を占めた．治療の合併症については現段階ではデータの検討中であるが，死亡率はきわめて低く，重篤な合併症発生率は5%より少なくなる見込みである．治療に関係ある術後の障害の原因として最も多いものは穿通枝の障害であり，その他の合併症として多いのが硬膜下水腫であった．治療成績に影響する因子として瘤のサイズと部位が有意な因子となり得る．施設間の症例数による差も検討する予定であるが，中間値では有意差は認められなかった．

登録状況の整合性チェックのため，破裂例の検討と10施設の現地調査を行った．破裂例は瘤の形状・サイズ，予後等を検討している．現地調査は2002年8月～11月に施行され，10施設総数406例を検討し，402例の病歴およびX線フィルムを検討できた．患者の承諾書が40例で不明，既往歴の漏れが6%，瘤のサイズを2 mm以上誤記されているものが12例（3%），部位の誤記が3例に認められた．治療は192例（52%）になされていたが，治療後のRankin scaleの誤記が13例（7%），うち2ポイント以上の誤記が2例（1%）にみられた．以上の現地調査の評価では，著しい登録の不整合は認められていない．

今後さらに症例を集積および追跡し，さまざまな側面から瘤の破裂率や治療成績を検討する予定である．

考　察

未破裂脳動脈瘤の治療方針決定のためには，各症例における自然歴と治療のリスクを検討し，患者本人および家族に十分な説明を行い，それぞれの意向により決定しなければならない[1)3)4)]．これまでさまざまな未破裂脳動脈瘤自然歴の検討が行われているが，そのほとんどが後

Table 2 Difference of annual rupture rates between the results of ISUA 1998 and 2003[6)7)]

ISUIA 2003	<7 mm		7〜12 mm	13〜24 mm	25 mm〜
	Group I	Group II			
Cavernous IC (n=210)	0	0	0	3.0%	6.4%
AC/MC/IC (n=1,037)	0	0.3%	0.5%	2.9%	8 %
Post-Pcom (n=445)	0.5%	0.7%	2.9%	3.7%	10 %
ISUIA 1998	<10 mm			10〜24 mm	25 mm〜
Group I (n=727)	0.05%			1%	6.5%
Group II (n=722)	0.5%			1%	

ISUIA：International Study of Unruptured Intracranial Aneurysms. Group I：without history of SAH. Group II：with history of SAH

ろ向きの検討であり，1つの報告の症例数が少なく，信頼区間が広いという問題がある[10)15)18)]．治療成績に関しては効果や合併症判定の時期と尺度が報告ごとに異なり[9)13)]，施設間格差の報告もあるため，1施設からの報告はエビデンスとしての力が低い[2)]．また外科手技の結果の報告は，成績の良い施設の報告が多いという問題もあげられている[19)]．

最近報告されたISUIAの前向きデータ[7)]では，1991〜1998年までに4,060例が61施設において前向きに登録されている．このうち治療群は1,917例，自然歴経過観察群は1,962例（観察期間6,544人/年）である．経過観察群は症候性が11%であり，開頭治療群の16%，血管内治療群の34%と比較すると少なく，7 mm未満の小型の瘤が62%と多かった．この報告と1998年の報告の自然歴の相違をTable 2にまとめる．破裂率は1998年の報告において10 mm未満ではクモ膜下出血のない群では0.05%/年，ある群では0.5%/年であったが[6)]，今回の発表では双方合わせた7〜12 mmの群ではウイリス輪前方で0.5%/年，後方で2.9%/年であると報告され，大きさの分類方法は異なるが，かなり前回と異なる結果となった．一方小型の7 mm未満の瘤では出血既往のない前方瘤で0%，後方瘤で0.5%，クモ膜下出血既往群でそれぞれ0.3%，0.7%となった．したがって小型瘤ではクモ膜下出血の有無で有意に出血率が異なり，全体をみると，大きさと部位が瘤の自然歴に関与する重大な因子であるとしている．治療成績に関しては開頭術では10〜13%，血管内治療では7〜10%の重篤な合併症を併発したとしている．血管内治療群の予後が一般によいが，対象疾患の相違があり，また血管内治療では完全閉塞は51%の症例でのみ可能であった．長期の経過観察が必要であると結論している．著者らは前向きの群と後ろ向きの群に有意差はないとしているが，この報告は前向きの予後評価と後ろ向きの評価の重大な相違を示しており，きわめて重要な知見であるといえる．

従来のコホート研究より[5)8)11)]，本邦におけるクモ膜下出血の発症率と欧米における発症率の相違が指摘されており，未破裂脳動脈瘤の破裂率そのものが異なる可能性がある．またISUIAの治療のリスクに関して，高次機能評価を加えているとしても，きわめて高い治療合併症に関して，一般の本邦における治療リスクの報告とは大きく異なる[12)]．そこで本邦発の前向き大規模研究が企画されたのである．

以上の点を踏まえ，本調査では前向きに患者を登録し，患者特徴のさまざまな側面をグループ分けできるように情報を集めることとした．その情報には各施設の規模（年間症例数）や治療の基本方針，各症例における治療選択の理由も含めている．破裂の評価方法やその予後の記載，治療評価の時期・方法を画一化し，さらに合併症の理由などの情報も必須事項とした．このような情報を可能なかぎり多くの症例において前向きに集積し，さまざま側面からデータを解析することにより，客観的な他の報告とも比較・対照し得る情報を得ることを目指している．ただしこの調査は大規模調査であるので，当初Mini Mental State Examination（MMSE）の導入は困難と考えられ，初期のプロトコールには加えられていなかったが，2002年度後半からの治療群について，協力可能な施設においてはこの調査も追加している．

本調査の特徴として大学病院医療情報ネットワーク（UMIN）の協力のもとに，インターネットを用いたデータ登録システムを利用しており，登録施設75%の施設においてこのシステムから登録が行われている．登録項目数は方法の項で述べたが，すべてボタンチェック方式にて登録できるので，患者1人当たりの登録に要する時間は長くとも10分以下である．また入力された情報は電子情報であり統一基準に基づくデータであり，統合や比較がきわめて容易である．またデータの解析を迅速に行

うことができる．特に事務局における症例登録時の機密事項の漏洩・紛失・入力ミス，また費用を大幅に削減することができた．

しかし一方では，このような画一的な入力方法では個々のさまざまな特異事象の登録は不可能であり，破裂例等の検討を含め，特異な例の検討は，個々の症例について各施設調査担当者とコンタクトをとり，情報を収集している．

2002年度に，それまでのオンライン方式を中心としたデータ入力の正誤性，画像診断の正確性をチェックするため参加施設のうち10施設を抽出し，現地のデータを実地検証した．既往歴や瘤の記載・計測，術後の状況判定に大きな誤記は認められなかった．

これまで得られたデータは中間値であり，最終的な結果は2006年度の調査終了を待たねばならない．あくまで中間値であるが，総症例数の破裂率は0.5%以上，治療による重篤な合併症は5%以下となる見込みである．個々の症例における治療方針の決定のためには細かい分類によるそれぞれのリスクの検証が必要であり，そのためにはさらに多くの症例の検討が必要である．破裂の危険性を高める因子はサイズ，瘤の部位，多発性，高齢者，女性，喫煙などとなる可能性があり．

一方，治療の危険性もサイズの大きいもの，部位が脳底部のものなどがあげられる．したがって，一般に破裂リスクの高いものほど治療リスクが高くなるという，治療方針決定を困難とさせるジレンマが生じる．これは先に触れたISUIAの前向き研究の報告でも同様の傾向が指摘されている[7]．

今後さらに多くの症例の登録と漏れのない経過観察を目指すため，学会，地方会，E-mail送付などで徹底した調査協力を呼びかけてゆく計画である．

結　語

UCAS Japanの2003年4月の時点での中間結果を報告した．現在まで全国395施設から月150～200症例前後の新規登録を得て4,940例の症例登録，4,079人/年の経過報告を受けている．この貴重なデータをさらに確実かつ有意義なデータとするためには，さらに多くの施設の参加と参加施設担当者の徹底した経過登録への協力が不可欠である．

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