

Unruptured Cerebral Aneurysms in Elderly Patients

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Abstract

The prevalence of unruptured cerebral aneurysms (UCAs) in elderly patients is increasing in our aging population. UCA management in elderly patients has some difficulties, such as reduced life expectancy, increased comorbidities and treatment risks, and poor prognosis in case of rupture. In this review article, we summarize the most recent findings on the natural history, therapeutic options and treatment results for UCAs exclusively in elderly patients, and describe possible medical treatments for patients with UCAs.

Key words: elderly, natural history, treatment, unruptured cerebral aneurysm, outcome

Introduction

The global population is currently aging at an accelerating pace. In developed countries, more than 75% of people die after 75 years of age, and in Japan, which has the longest life expectancy, female life expectancy was 86 years in 2007.¹ The advancement and prevalence of neuroimaging modalities, such as computed tomography angiography (CTA) and magnetic resonance angiography (MRA), and a prolonged average life expectancy have led to increased detection of unruptured cerebral aneurysms (UCAs) in Japan. The Unruptured Cerebral Aneurysm Study of Japan (UCAS Japan) included a total of 5,720 patients and 1,577 patients (28%) were over 70 years of age.² Elderly patients with UCAs have some intrinsic difficulties, such as decreased life expectancy, increased presence of comorbid disease, increased surgical treatment risks, and poor prognosis for elderly patients with ruptured aneurysms.³ In this article, we review the natural history of UCAs in elderly patients, surgical results of UCAs in elderly patients, and feasibility of medical treatment for patients with UCAs.

Natural History of UCAs in Elderly Patients

Prevalence of UCAs

Iwamoto et al. evaluated 1230 consecutive autopsy cases from 1962 to 1991 in the Hisayama study and they reported that the prevalence of UCAs was

2.6%.⁴ They demonstrated that the prevalence of UCAs increased with age and that it was highest in patients 80 years of age or older (4.8%).⁴ Harada et al. revealed that the prevalence of UCAs detected by MRA was 3.2% and it increased with age in both sexes in 8696 healthy asymptomatic Japanese adults from 2010 to 2012.⁵ However, a meta-analysis for prevalence of UCAs showed that the prevalence was lower in patients younger than 30 years of age, but not in patients aged 30–39 years, 40–49 years, 50–59 years, 60–69 years, and 70–79 years compared with patients aged 80 years or older (prevalence 3.0%).⁶ The influence of age on the prevalence of UCAs remains controversial.

Risk factors for UCA rupture

The natural history of UCAs in the general populations was reported in large prospective studies.^{2,7–11} The International Study of Unruptured Intracranial Aneurysms (ISUIA) indicated that the size (7 mm or larger) and location (tip of basilar arteries, internal carotid-posterior communicating arteries [IC-PCoM]) were significant risk factors for rupture.⁷ UCAS Japan showed that the annual rate of rupture was 0.95% and that UCAs larger than 7 mm, located in the anterior communicating and IC-PCoM, and with a daughter sac had independent risk factors for rupture in the general population.² It is unclear whether the natural history of UCAs in the general population is the same as that in elderly patients. Clarifying the natural history of UCAs in elderly patients has an important role when considering therapeutic strategies in a clinical setting. Hishikawa et al.

performed a pooled analysis of prospective cohorts using three studies (UCAS Japan, UCAS II, and the study at the Jikei University School of Medicine), all of which were representative of large-scale studies performed in Japan to identify risk factors for UCA rupture in elderly patients 70 years of age or older.¹²⁾ A total of 1896 patients with 2227 UCAs were evaluated during a mean follow-up period of 802.7 days, and the annual rupture rate was reported to be 1.6% (68 subarachnoid hemorrhages/4167 patient-years) in the study.¹²⁾ Additionally, it was demonstrated that the cumulative rates of rupture in patients older than 80 years of age were significantly higher than in those of patients aged 70–79 years.¹²⁾ In patients aged 80 years or older, aneurysms 7 mm or larger and IC-PCoM A aneurysms were the independent predictors for UCA rupture in elderly patients.¹²⁾ The larger aneurysms are a common risk factor for UCA rupture in the general population and elderly patients. Aneurysm size was significantly related to patients' age in the UCAS Japan, which may be one possible explanation for the higher annual rupture rate in elderly patients.²⁾ The UCAS Japan showed that elderly patients had significantly more posteriorly located aneurysms, and only IC-PCoM A aneurysms remain an independent risk for rupture in elderly patients, probably because of the difference in the distribution of aneurysms regarding location and age.^{2,12)} The investigation by Hishikawa et al. identified some important findings and problems, such as a higher rupture rate in elderly patients, and a significant risk factor for rupture in patients aged 80 years or older. The annual rupture rate of UCAs in elderly patients is higher than that reported in the general Japanese population and non-Japanese populations.^{2,7,9,11,12)} Wermer et al. reported that increased age was one of the risk factors for UCA rupture,¹³⁾ while some studies demonstrated that age was inversely related to UCA rupture.^{9,11)} It is unclear how age itself relates to the biological mechanisms of UCA rupture. Table 1 shows a summary of the annual rupture rate and risk factors for UCA rupture in large cohort studies. It is noteworthy that the only report by Hishikawa et al. exclusively included elderly patients in their investigation; however, this study had several limitations. First, the difference in the frequency of surgical intervention among patients aged 70–79 years (28%) and patients aged 80 years or older (4%) may have been due to age bias. Second, comorbid diseases were not evaluated in this study. To assess the natural history of UCAs in elderly patients more accurately, it would be meaningful to evaluate the influence of comorbid

diseases, such as hyperlipidemia, diabetes mellitus, polycystic kidney disease, cerebral infarction, ischemic heart disease, and malignant tumor, on the risk of UCA rupture in further studies.

Therapeutic Options for UCAs in Elderly Patients

Comparison between surgical clipping and coil embolization

Repairing the UCAs in elderly patients involves selecting between surgical clipping and coil embolization, and the best option remains controversial because there is no randomized clinical trial (RCT) for UCAs. The International Subarachnoid Aneurysm Trial (ISAT) is an RCT that was undertaken to compare the safety and efficacy of coil embolization with surgical clipping in subarachnoid hemorrhage (SAH) patients for whom it was safe to undergo either treatments.¹⁴⁾ According to the ISAT subgroup analysis of 278 SAH elderly patients who were 65 years or older, coil embolization should probably be the favored treatment of a ruptured internal carotid artery (ICA) and IC-PCoM A aneurysms, whereas surgical clipping should be the treatment of choice for ruptured middle cerebral artery aneurysms.¹⁵⁾ However, these results cannot be simply applied to the UCAs in elderly patients because there are some differences in the natural history and aneurysm characteristics between ruptured aneurysms and UCAs. In the absence of an RCT comparing these two surgical modalities, data based on non-RCTs should be used to decide on therapeutic options for elderly patients with UCAs.

Some retrospective and prospective cohort studies have compared the outcomes in elderly patients with UCAs, who were treated using surgical clipping with those who were treated using coil embolization.^{16–22)} Mahaney et al. reported that poor neurological outcome from aneurysm- or procedure-related morbidity and mortality was significantly higher in the surgical group for patients older than 65 years of age: 19.0%, compared with 8.0% in the endovascular group in the subanalysis of 4059 patients in ISUIA.²⁰⁾ Bekelis et al. revealed that there was no difference between coil embolization and surgical clipping for 1-year postoperative mortality or 90-day readmission rate, but surgical clipping was associated with a higher rate of discharge to a rehabilitation facility and a longer length of stay for elderly patients.²²⁾ The study of the National Inpatient Sample in the United States showed that patients 65–79 years of age who underwent coil embolization had significantly lower morbidity (6.9% versus 26.8%) and mortality (0.8% versus 2.0%)

Table 1 Annual rupture rates and risk factors for UCA rupture in large cohort studies

Study and year of publication	Country	Inclusion criteria	No. of patients	No. of aneurysms	FU durations (mean)	Age (years) (mean \pm SD)	Aneurysm size (mm) (mean \pm SD)	Annual rupture rate (%)	Risk factors for UCA rupture
ISUIA, ⁷⁾ 2003	USA, Canada, and Europe	General population, ≥ 2 mm	1692	2686	4.1 years	55.2 \pm 13.1	7.4 \pm 6.9	0.8	≥ 7 mm, BA tip, IC-PCoM A
Ishibashi, et al., ⁸⁾ 2009	Japan	General population	419	529	905.3 days	60.8 \pm 11.4	4.5 \pm 3.5	1.4	History of SAH, ≥ 10 mm, Posterior circulation
SUAve study, ⁹⁾ 2010	Japan	General population, < 5 mm	374	448	41.0 months	61.9 \pm 10.3	3.3 \pm 0.9	0.54	< 50 yrs, Hypertension, ≥ 4 mm, Multiplicity
UCAS Japan, ²⁾ 2012	Japan	General population, ≥ 3 mm	5720	6697	635.9 days	62.5 \pm 10.3	5.7 \pm 3.6	0.95	≥ 7 mm, ACoM A, IC-PCoM A, Irregular shape
Juvela, et al., ¹¹⁾ 2013	Finland	General population	142	181	21.6 years	41.8 \pm 10.8	5.1 \pm 3.7	1.1	Age inversely related, Smoking, ≥ 7 mm, ACoM A
Hishikawa, et al., ¹²⁾ 2015	Japan	Elderly patients (> 70 years)	1896	2227	802.7 days	74.3 \pm 3.9	6.2 \pm 3.9	1.6	> 80 years, ≥ 7 mm, IC-PCoM A

ACoM A: anterior communicating artery, BA: basilar artery, FU: follow-up, IC-PCoM A: internal carotid-posterior communicating artery, ISUIA: International Study of Unruptured Intracranial Aneurysms, SAH: subarachnoid hemorrhage, SD: standard deviation, SUAve: Small Unruptured Intracranial Aneurysm Verification, UCAs: unruptured cerebral aneurysms, UCAS: Unruptured Cerebral Aneurysm Study.

compared with patients who underwent clipping, and that patients aged 80 years or older who were treated by coil embolization also had significantly lower morbidity (9.8% versus 33.5%) and mortality (2.4% versus 21.4%) compared with patients treated using surgical clipping.¹⁸⁾ In this study, only 15% of patients aged 80 years or older were treated by surgical clipping and the morbidity and mortality rates for these patients were extremely high. This was probably because these cases were considered not to be amenable to coil embolization and were at high risk for treatment complications. According to the meta-analysis of elderly patients who underwent coil embolization to treat UCAs, the perioperative stroke and mortality rate was 4% and 1%, respectively, and the rate of good clinical outcome at 1 year was 93%.²³⁾ These data indicate that coil embolization may be the best option to treat UCAs in elderly patients. There are some explanations for worse outcomes of surgical clipping for UCAs in elderly patients. First, perioperative stroke in surgical clipping was directly associated with worse outcomes in elderly patients.²⁰⁾ Second, increased pain and slower mobilization as a result of surgical clipping, which is a more invasive procedure, may lead to more secondary medical complication in elderly patients.²²⁾

The retrospective studies comparing surgical clipping and coil embolization have some important limitations in interpreting the results. First, these studies are retrospective and patients were not randomized to treatment. Therefore, there is a significant potential for selection bias that might have affected the outcomes of surgical clipping or coil embolization.¹⁸⁾ Second, the findings from these studies are based on a specific population of elderly patients with UCAs, and these findings may not be generalizable to other populations.²²⁾ RCTs comparing surgical clipping, coil embolization, and observation in different population are necessary to decide upon an evidence-based therapeutic management plan for elderly patients with UCAs.

Flow diverters for UCAs in elderly patients

Flow diverters are recently developed endovascular devices for complex aneurysms. The meta-analysis including 29 studies showed that treatment with flow diverters was feasible and effective with high complete occlusion rates.²⁴⁾ Recently, flow diverter devices Pipeline Flex (Medtronic), was introduced in Japan, and this device can be used for proximal ICA aneurysms larger than 10 mm. In the future, the number of elderly patients undergoing aneurysm embolization with a flow diverter is expected to

increase. The outcomes of elderly patients with UCAs that are treated using flow diverters should be elucidated because the mechanisms by which flow diverters repair UCAs are different from those of coil embolization. Brinjikji et al. reported that the overall complication rates for the Pipeline Embolization Device (PED) treatment in highly selected elderly patients, 70 years of age or older were acceptably low and concluded that age alone should not be considered an exclusion criteria when PED treatment is considered.²⁵⁾

Indication for treatment of UCAs in elderly patients

When deciding whether to treat or observe UCAs in elderly patients, several factors must be considered, such as precise knowledge of natural history, treatment-related risks, the individual's comorbid diseases and life expectancy, and the wishes of the patients and their families. Indication for the treatment of UCAs in elderly patients should be determined individually. Data based on prospective cohorts identifying risk factors for UCA rupture and non-RCTs comparing surgical clipping and coil embolization indicate that elderly patients with aneurysms 7 mm or larger, or those with IC-PCoM A aneurysms may be candidates for coil embolization if they are considered to be amenable to safe coil embolization.

Potential medical treatment for UCAs

Cerebral aneurysm formation involves endothelial dysfunction, a mounting inflammatory response, vascular smooth muscle cell phenotypic modulation, extracellular matrix remodeling, and subsequent cell death and vessel wall degradation.²⁶⁾ It has also been reported that dental infection caused by endodontic and periodontal bacteria may contribute to the pathophysiology of ruptured cerebral aneurysms.²⁷⁾ Recent studies have shown that chronic inflammation plays a role in the development or rupture of cerebral aneurysms and experimental therapies targeting different molecular inflammatory effectors in animal models were shown to be efficacious and promising.^{28–32)} If clinical evidence that anti-inflammatory drugs prevent UCAs from bleeding or growing is provided, medical treatment for elderly patients with UCAs could be the first-line therapy. In this section, we introduce some anti-inflammatory drugs for cerebral aneurysms that were used in experimental studies.

Statins

Statins have anti-inflammatory effects in various vascular diseases. Some types of statins have been experimentally investigated and reported to have

protective effects on the cerebral aneurysm formation and progression.^{28,29,31)} Aoki et al. demonstrated that pitavastatin had a suppressive effect on cerebral aneurysm progression through the inhibition of nuclear factor- κ B activation in the aneurysm walls in a rat model.²⁹⁾ In Japan, a multi-center prospective randomized trial called Small Unruptured Aneurysm Verification-Prevention Effect against Growth of cerebral Aneurysm Study Using Statins (SUAVE-PEGASUS) is currently ongoing. This study is evaluating whether statins have protective effects on human UCAs.

Aspirin

Hasan et al. performed a subanalysis of 271 subjects enrolled into ISUIA, and they showed that patients with UCAs who used aspirin three times weekly to daily had a significantly lower risk of rupture compared with those who had never taken aspirin.³²⁾ They expected that aspirin may potentially be a therapeutic agent to prevent cerebral aneurysm growth and rupture by inhibiting several inflammatory mediators.³²⁾

Free radical scavenger (Edaravone)

Aoki et al. demonstrated that oral intake of edaravone in a rat model of cerebral aneurysms effectively inhibited reactive oxygen species and medial degradation in the aneurysm wall, which suggests that edaravone has a protective effect against rupture.³⁰⁾ Edaravone is widely used for patients with acute cerebral infarction in Japan, and it is feasible options for UCA.

Tetracycline derivatives

Makino et al. demonstrated that tetracycline derivatives (doxycycline and minocycline) reduced the incidence of aneurysmal rupture through their general anti-inflammatory effects in a mouse model of intracranial aneurysm.³³⁾

Conclusions

We reviewed recent findings on the natural history, therapeutic options, and treatment results of UCAs in elderly patients and described potential medical treatments for UCAs, based on experimental studies. We expect that this article will help clinicians to decide the therapeutic strategy for UCAs in elderly patients in a clinical setting.

Conflicts of Interest Disclosure

All authors who are a member of the Japan Neurosurgical Society (JNS) have registered online self-reported

COI Disclosure Statement Forms through the website. The authors have no interests to declare.

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