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เพศและการสูงวัยต่อแนวโน้มการแตกของหลอดเลือดแดงสมองโป่งพอง: การศึกษาย้อนหลังด้วย 3DRA

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Predisposition of Sex and Aging to Ruptured Intracerebral Aneurysms: a Retrospective Study by 3DRA

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หลักการและวัตถุประสงค์: ผู้สูงอายุและสตรีวัยหมดประจำเดือนมีแนวโน้มหลอดเลือดแดงสมองโป่งพองแตก ปัจจุบันเอกซเรย์หลอดเลือดสามมิติ (3DRA) เป็นวิธีมาตรฐานตรวจพยาธิสภาพหลอดเลือด การศึกษานี้จึงมีวัตถุประสงค์ใช้ 3DRA หาความชุกผู้ป่วยเลือดออกใต้เยื่อหุ้มสมองชั้นกลางจากหลอดเลือดแดงสมองโป่งพองแตก ในแง่เพศ อายุ จำนวนหลอดเลือดโป่งพอง และตำแหน่งหลอดเลือดแตก

วิธีการศึกษา: ศึกษาย้อนหลังโดยใช้ 3DRA ของผู้ป่วยเลือดออกใต้เยื่อหุ้มสมองชั้นกลางที่ไม่ได้บาดเจ็บศีรษะ เปรียบเทียบจำนวนระหว่างกลุ่มที่มีและที่ไม่มีหลอดเลือดแดงสมองโป่งพอง วิเคราะห์จำนวนผู้ป่วยกลุ่มหลอดเลือดโป่งพองเกี่ยวกับเพศ อายุ จำนวนหลอดเลือดโป่งพอง และตำแหน่งหลอดเลือดแตก

ผลการศึกษา: มีหลอดเลือดโป่งพองแตก 91จาก 126 ราย หรือร้อยละ 72.22 ใน 91 รายเป็นหญิงร้อยละ 71.43 โดยมีความชุก 2.5 เท่าของชาย กลุ่ม 50-79 ปี มีจำนวนมากกว่ากลุ่มอายุ 20-49 รายที่ปรากฏหลอดเลือดโป่งพองหลายตำแหน่งมีร้อยละ 14.29 โดยพบในหญิงมากกว่า และรายที่หลอดเลือดแตกนอก circle of Willis (CW) มีร้อยละ 31.87

สรุป: ผู้ป่วยหลอดเลือดแดงสมองโป่งพองแตกมีความชุกมากในผู้สูงอายุโดยเฉพาะสตรีวัยหมดประจำเดือน ความชุกของ

Background and Objectives: Elderly people and postmenopausal women tend to have ruptured intracranial aneurysm. At present, three-dimensional rotational angiography (3DRA) is the new gold standard to detect vascular pathology. Therefore, this study aimed to investigate the prevalence of non-traumatic subarachnoid hemorrhage (SAH) patients with ruptured intracranial aneurysms regarding to sex and age of the patients, number of ruptured and unruptured aneurysms and ruptured aneurysm sites, based on 3DRA.

Methods: This retrospective study was performed on 3DRA of non-traumatic SAH patients. The numbers of patients in aneurysmal and non-aneurysmal groups were compared. The numbers of intracranial aneurysmal patients regarding to sex, age, all ruptured and unruptured aneurysms, and ruptured aneurysm sites were recorded and analyzed.

Results: The prevalence of subjects with ruptured intracranial aneurysm was 72.22% of 126 enrolled SAH patients. Of 91 intracranial aneurysmal subjects, the prevalence of females was 71.43%, as high as 2.5 times that of male. The percentage of aneurysmal patients aged between 50-79 years was higher than that of the subjects

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รายโป่งพองหลายตำแหน่งและรายที่มีตำแหน่งแตกนอก CW มีมากกว่าการศึกษาที่ผ่านมา

aged between 20-49 years. The prevalence of subjects with multiple aneurysms appeared in 14.29% of aneurysmal patients and predisposed to the female. The patients with ruptured aneurysms located outside the circle of Willis (CW) comprised 31.87%.

Conclusion: The prevalence of SAH patients with ruptured intracranial aneurysms was high in elderly people, especially postmenopausal women. This study also revealed the higher percentage of SAH patients with multiple aneurysms and the higher frequency of patients with ruptured aneurysms located outside the CW than the previous reports.

Keywords: subarachnoid hemorrhage, three-dimensional rotational angiography (3DRA), postmenopausal women, aging, multiple intracranial aneurysms

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Introduction

Subarachnoid hemorrhage (SAH) represents a neurologic emergency characterized by extravasation of blood into the subarachnoid space enclosing the brain. There has been a study reporting that 85% of non-traumatic SAH occurs from a ruptured cerebral aneurysm, whereas 10% of them represent non-aneurysmal perimesencephalic SAH, a relatively harmless condition with a low risk of re-bleeding, and the remaining 5% occurs by various rare causes[1].

The intracranial aneurysm (also termed cerebral aneurysm or brain aneurysm) is a pathological dilatation or ballooning of the cerebral arterial wall. It commonly develops at arterial branching sites which was mostly established on the circle of Willis (CW)[1]. Rupture of the aneurysm causes aneurysmal SAH, and the risk of the rupture tends to increase in women and aged persons[2,3]. The occurrence rate of re-bleeding prior to the aneurysm closure ranged from 8%-23% of total patients within 72 hours after the aneurysmal rupture[4], and 50% of them within 6 months after the initial occurrence with the mortality rate of 70%[5].

Moreover, multiple intracranial aneurysms are frequent, with a prevalence of 19%-34% of SAH patients as cited by Jeon and coworkers[6]. Accurate localization of aneurysmal rupture sites in patients with multiple cerebral aneurysms is difficult in clinical practice, and it is critical to determine which arterial site is mainly ruptured, because it is impractical to manage all aneurysms in a single craniotomy. Among harmful sequelae of SAH, undiagnosed ruptures may result in re-bleeding and the affected patients underwent noticeably higher rates of morbidity and mortality because the true rupture site is untreated[7].

Detailed knowledge of the intracranial aneurysm is of paramount importance, but most of the previous reports were based on surgery, autopsy and digital subtraction angiography (DSA) with various prevalence of 54.35%[8], 57.6%[9], 76%[10], and 85%[1]. Although the gold standard for detecting the vascular pathological lesions at present is a three-dimensional rotational angiography (3DRA) which is annotated to discover additional small aneurysms[11], reports of the intracranial aneurysm based on 3DRA are scanty.

Hence, this study aimed to investigate the prevalence of non-traumatic SAH patients with ruptured intracranial aneurysms regarding to sex and age of ailed patients, the number of ruptured and unruptured aneurysms and the ruptured aneurysm sites, based on 3DRA.

Materials and Methods

1. Sample collection: This retrospective study was performed on 3DRA data of patients with non-traumatic SAH who underwent angiography at the Faculty of Medicine, Khon Kaen University between January 2015 and June 2015. Exclusion criteria were: 1) extracranial aneurysms, 2) dissecting or traumatic aneurysms, or 3) aneurysms in association with an arteriovenous malformation.

The included patients were divided into 2 main groups, aneurysmal and non-aneurysmal ones. The aneurysmal group represents patients with SAH caused by intracranial aneurysmal rupture, while the non-aneurysmal group represents patients with non-traumatic SAH affected by other causes. Sex and age of the total patients are recorded. The number of patients in each of these two groups were recorded and compared. Then, the subjects in the aneurysmal group were investigated in details. The age and sex of patients in the aneurysmal group, the number of all ruptured and unruptured aneurysms and sites of the ruptured aneurysms were recorded and analyzed.

This study was performed under the Khon Kaen University Ethics Committee in Human Research (HE591192). All records and information of the patients were anonymized.

2. Image technique: Angiography was rendered on a biplane neuroangiographic unit (Siemens Artis Zee Biplane). A complete cerebral 3DRA was performed on the biplane system with an 8- second 180° rotational run and an injection of contrast material of 3- to 4-milliliters per second into the vertebral or the internal carotid arteries.

Results

A total of 126 non-traumatic SAH patients were included in the study. The mean age of SAH patients was 56.21 ± 12.82 years with the age range of 9-84. The SAH patients comprised 42 males (33.33%) and 84 females (66.67%), along with 91 aneurysmal patients (72.22%) and 35 non-aneurysmal patients (27.78%) as shown in Table 1.

Table 1 Subarachnoid hemorrhage (SAH) patients regarding to sex and intracranial aneurysms

SAH patients	Number (%)
Sex	
Male	42 (33.33)
Female	84 (66.67)
Aneurysm	
Present	91 (72.22)
Absent	35 (27.78)
Total	126 (100)

Of 91 intracranial aneurysmal SAH patients, the sex, the age ranges, the numbers of all aneurysms and the sites of ruptured aneurysms were shown in Table 2. The patients were composed of 26 males (28.57%) and 65 females (71.43%). The mean age of all the aneurysmal patients was 56.41 ± 12.07 years with the age range of 22-79, while that of male was 54.04 ± 10.10 years with the age range of 27-68 and that of female was 57.35 ± 12.72 years with the age range of 22-79.

Dividing the aneurysmal patients into 2 subgroups, i.e., subgroups with the age ranges of 20-49 and 50-79 years, the prevalence of the patients at the age range of 20-49 was 27.47%, 7.69% were male and 19.78 % were female. The percentage of the patients at the age range 50-79 was 72.53%, 20.88% were male and 51.65% were female.

Women outnumbered men in the prevalence of ruptured aneurysms in all decades of life except the same percentage in the third decade. The highest frequencies were 13.19% for male at the age of 50s and 20.88% for female at the age of 60s (Figure 1).

Table 2 Sex, age ranges, numbers of all aneurysms and ruptured aneurysm sites of intracranial aneurysmal subarachnoid hemorrhage patients

	Male	Female	Total
	Number (%)	Number (%)	Number (%)
Age 20-49 years	**7 (7.69)**	**18 (19.78)**	**25 (27.47)**
20-29	1 (1.10)	1 (1.10)	2 (2.20)
30-39	1 (1.10)	5 (5.49)	6 (6.59)
40-49	5 (5.49)	12 (13.19)	17 (18.68)
Age 50-79 years	**19 (20.88)**	**47 (51.65)**	**66 (72.53)**
50-59	12 (13.19)	17 (18.68)	29 (31.87)
60-69	7 (7.69)	19 (20.88)	26 (28.57)
70-79	-	11 (12.09)	11 (12.09)
Total	**26 (28.57)**	**65 (71.43)**	**91 (100)**
Number of aneurysms			
Multiple	5 (5.49)	8 (8.79)	13 (14.29)
Single	21 (23.08)	57 (62.64)	78 (85.71)
Total	**26 (28.57)**	**65 (71.43)**	**91 (100)**
Sites of ruptured aneurysms: inside circle of Willis			
Anterior communicating artery	6 (6.59)	18 (19.78)	24 (26.37)
Right posterior communicating artery	3 (3.30)	13 (14.29)	16 (17.58)
Left posterior communicating artery	3 (3.30)	9 (9.89)	12 (13.19)
Tip of basilar artery	2 (2.20)	4 (4.40)	6 (6.59)
Left internal carotid artery	-	2 (2.20)	2 (2.20)
Right internal carotid artery	1 (1.10)	-	1 (1.10)
Right A1 segment of anterior cerebral artery	1 (1.10)	-	1 (1.10)
Total	**16 (17.58)**	**46 (50.55)**	**62 (68.13)**
Site of ruptured aneurysms: outside circle of Willis			
Left middle cerebral artery	3 (3.30)	2 (2.20)	5 (5.50)
Right middle cerebral artery	-	4 (4.40)	4 (4.40)
Left posterior cerebral-superior cerebellar artery	1 (1.10)	2 (2.20)	3 (3.30)
Right anterior choroidal artery	-	3 (3.30)	3 (3.30)
Left anterior choroidal artery	1 (1.10)	-	1 (1.10)
Paraclinoid segment of internal carotid artery	-	2 (2.20)	2 (2.20)
Pericallosal artery	-	2 (2.20)	2 (2.20)
Right posterior inferior cerebellar artery	-	2 (2.20)	2 (2.20)
Left posterior inferior cerebellar artery	1 (1.10)	-	1 (1.10)
Right superior cerebellar artery	-	1 (1.10)	1 (1.10)
Right ophthalmic artery	-	1 (1.10)	1 (1.10)
Left ophthalmic artery	1 (1.10)	-	1 (1.10)
Superior hypophyseal	1 (1.10)	-	1 (1.10)
Left A2 segment of anterior cerebral artery	1 (1.10)	-	1 (1.10)
Trunk of basilar artery	1 (1.10)	-	1 (1.10)
Total	**10 (10.99)**	**19 (20.88)**	**29 (31.87)**

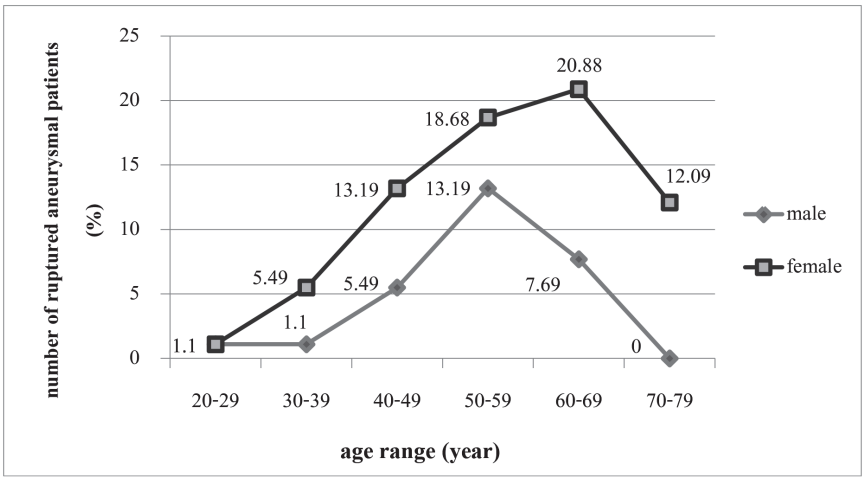

Figure 1 Percentages of male and female aneurysmal patients in consecutive decades of life

A total of 109 ruptured and unruptured intracranial aneurysms were revealed in 91 intracranial aneurysmal patients. Single aneurysm occurred in 78 patients (85.71%), 23.08% were male (the age range of 27-68 years) and 62.64% were female (the age range of 22-77). Multiple aneurysms were found in 13 patients (14.29%), 5.49% were male (the age range of 50-65 years) and 8.79% were female (the age range of 51-79). Among the 13 patients harboring multiple aneurysms, 10 patients (4 males, 6 females) had two aneurysms, 2 patients (1 male, 1 female) had three and 1 patient (female) had five aneurysms.

Ruptured aneurysms located inside the CW were revealed to occur in 68.13% of aneurysmal patients (17.58% were male and 50.55% were female), whereas ruptured aneurysms outside the CW occurred in 31.87% of aneurysmal ones (10.99% were male and 20.88% were female). Angiographs of aneurysms at sites with high prevalence were shown in Figure 2. Ruptured aneurysms located inside the CW were frequently found at the anterior communicating artery (ACoA) with the occurrence of 26.37% of the ruptured aneurysmal cases, at the right posterior communicating artery (Rt PCoA) with 17.58%, at the left posterior communicating artery (Lt PCoA) with 13.19% and at the tip of basilar artery (BA tip) with 6.59%. The aneurysms outside the CW were frequently located at the left middle cerebral artery (Lt MCA) in 5.50% and the right middle cerebral artery (Rt MCA) in 4.40%.

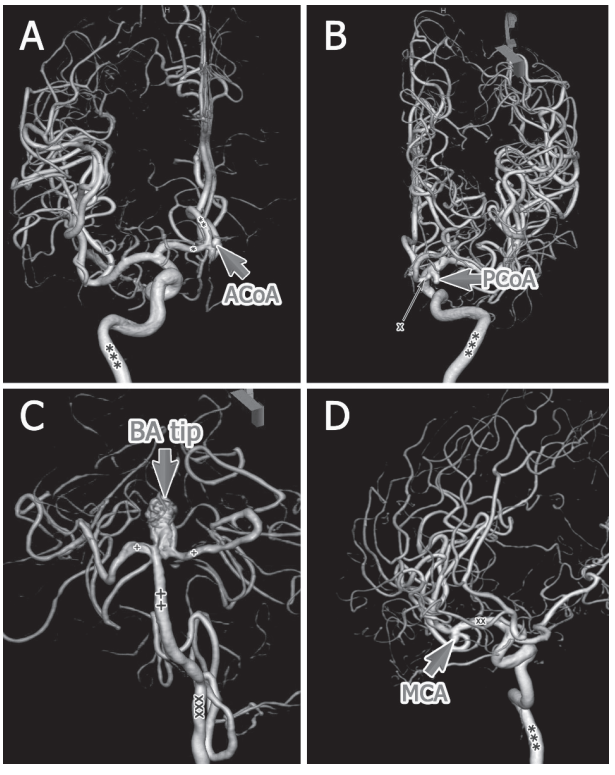

Figure 2 Angiographs of aneurysms at sites with high prevalence A: anterior communicating artery (ACoA) B: posterior communicating artery (PCoA) C: tip of basilar artery (BA tip) D: middle cerebral artery (MCA) *A1 segment of anterior cerebral artery, **A2 segment of anterior cerebral artery, *** Internal carotid artery, x = Posterior communicating artery, xx = Middle cerebral artery, xxx = Vertebral artery, + = Posterior cerebral artery, ++ = Basilar artery

Discussion

The present study with 3DRA showed that intracranial aneurysmal rupture was the major cause of non-traumatic SAH. As cited by Rossitti and Löfgren[12], intracranial arteries were probably more susceptible to the aneurysm formation than extracranial arteries of the same diameter because of their thinner and stiffer arterial walls as well as lacking of external elastic lamina supporting the walls. Moreover, the aneurysm formation might be related to branching characteristics of the cerebral arteries which provoked a hemodynamic stress[13-15].

The frequency of aneurysmal rupture in this study, 72.22% of non-traumatic SAH patients, was compatible with 76% of aneurysmal SAH subjects diagnosed by angiography, surgery, or autopsy in a previous study review of the ACROSS Group in Australia and New Zealand[10]. Nevertheless, the present prevalence was discordant with 54.35% - 57.60% in the other studies examined by DSA[8,9]. Angiographic modalities seemed to be a possible reason for this incompatibility. Van Rooij and coworkers[11] annotated the efficacy of 3DRA in investigation of small additional aneurysms and discovering of some target aneurysms which were missed out on DSA. Van Gijn and colleagues[1] reported that as high as 85%of SAH cases were caused by ruptured aneurysms. They criticized that the high prevalence in the previous studies was overestimated until the cerebral imaging provided a correct distinction between subarachnoid hemorrhage occupying within subarachnoid space and intracerebral hemorrhage occurring within the brain.

The frequency of female aneurysmal subjects in this study was as high as 2.5 times that of male, in accord with the previous studies stating that female were significantly more susceptible to aneurysm formation[8,10,16-19]. Patients at higher ages, especially of female, tended to have an increased prevalence of intracranial aneurysmal rupture[2]. The mean age of all patients with ruptured aneurysms in the present study was 56.41 ± 12.07 years. That of female patients was a little bit higher than that of male, the mean age of female was 57.35 ± 12.72 and that of male was 54.04 ± 10.10 years. With increasing age, the cerebral arteries are possibly more prone to develop defects of the muscular layer of the arterial wall[12].

In the present study, no aneurysms were found in the first two decades of life. The percentage of aneurysmal patients in both males and females steadily increased from the third decade until it reached the highest peak at the age 50s in male and 60s in female. The decrease of the prevalence thereafter may be due to a missing follow-up appointment, a patient's mortality from re-bleeding or other causes of death in old ages. Similar findings were revealed in a previous study by Bhat and coworkers[8] stating that SAH patients were predominant in the age group of 41-60 years and most of them were aneurysmal in origin. It is noticeable that the percentages of female aneurysmal patients were higher than that of male in every decade of life.

The age of natural menopause varies extensively between women across different ethnic groups. Between 50 and 59 years of age, the menopause typically occurs and the estrogen level starts to decrease[20]. The mean age of natural menopause in a group of Thai people was reported at 48.76 ± 4.33 years[21]. Data obtained from 26 countries revealed that the mean age of menopause was 49.24 ± 1.73 years[22]. Consequently, this study classified the age from 50 years and older as the postmenopausal period for female subjects. Dividing the aneurysmal patients into 2 groups of age range, i.e., 20-49 and 50-79 years, the occurrence of aneurysm was highest in female subjects with the age range of 50-79 years, the postmenopausal women. A considerable number of studies also revealed that female, mostly at the postmenopausal period, had a high risk of intracranial aneurysm formation and SAH[8,17,23-24].

By this 3DRA examination, multiple intracranial aneurysms were found in 13.40% of the aneurysmal subjects, and this occurrence was higher than that of the previous studies in SAH patients on whom surgeries were performed[25,26]. Phuenpathom and colleagues[25] reported the prevalence of multiple intracranial aneurysms to be 6.5 % of patients with intracranial aneurysmal rupture, and Navalitloha and coworkers[26] reported it to be 8.7 % of them. The restriction to a part of the cerebral vasculature during the surgical exploration may be the possible reason to explain the lower percentages[11].

The prevalence of multiple intracranial aneurysms in female was also higher than that in male as reported by others[27-30]. Hormonal factor, the deprivation of estrogen, was implicated to be a significant contribution of the intracranial aneurysm formation and growth in postmenopausal women[31-32]. Men encounter fewer risks because of no estrogen withdrawal as women do. Estrogen might play an important role in vascular and aneurysmal integrity through the control of collagen content and the vascular wall thickness[31]. Consequently, loss of these effects such estrogen withdrawal at the postmenopausal period tends to increase the risk of SAH in women.

Most of aneurysms examined in the present study were located inside the CW, which was in accord with the previous reports[9,33]. This suggests that aneurysms may develop at the sites of arterial branching which has been mostly found on the CW[1]. Predominant aneurysmal sites were ACoA, PCoA and MCA, as corresponding to the other studies[9,34] but the percentage of the aneurysmal patients with BA tip site in this study was 6.59 %, higher than 2.6%-5.9% reported by those previous ones. Although ACoA was the aneurysmal site of the highest rate in this study, 26.37% of the aneurysmal patients, the frequency was lower than that in the previous literatures[9,34]. The occurrence of aneurysmal rupture on ACoA reported by Kitkhuandee and colleagues[9] was 35.5% and that by Duong and coworkers[34] was 27.6%. The application of 3DRA in this study was the most plausible reason for this difference. The greatest benefit of 3DRA was the high ability to detect very small arteries and aneurysms in all directions including difficult-to-reach areas for surgery and the ones outside the CW. This may lead to a higher percentage of the aneurysms outside the CW and a lower percentage of ACoA aneurysms proportionally. Kasuya and coworkers[35] described that ACoA site had a smaller A1-A2 junction, leading to a higher hemodynamic stress and the aneurysm formation[37]. The efficacy of ACoA vasodilatation is also limited comparing to the rest of intracranial arteries because it is the only cerebral artery developing from the plexiform blood vessels[36].

Accordingly, elderly people especially menopausal women as well as patients with the aneurysm location on ACoA, PCoA, BA tip and MCA should secure additional attention during follow-up imaging and surgery.

Notably, this study based on 3DRA also showed the higher frequency of SAH patients with multiple aneurysms than the other reports of SAH patients on whom surgeries were performed[25,26], and the higher prevalence of ruptured aneurysms outside the CW than the previous report which DSA was carried out[9]. These findings should be considered to develop optimal investigation and treatment for aneurysmal SAH patients, leading to lower rates of morbidity and mortality.

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