Original Article

Natural History of Angiogram-Negative Non-Traumatic Subarachnoid Hemorrhage in Northeastern, Thailand

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Objective: Non-traumatic subarachnoid hemorrhage [SAH] is mostly caused by a ruptured intracnial aneurysm. A conventional or three dimension [3D] digital subtraction angiography [DSA] is a gold standard radiographic modality to detect intracranial aneurysm. Those SAH patients with negative DSA or 3D-DSA are called angiogram-negative non-traumatic SAH. A natural history and prevalence of this condition in northeastern Thailand are limited.

Materials and Methods: The present study was conducted at Srinagarind Hospital or Khon Kaen University Hospital. The study period was between January 2014 and June 2016. The inclusion criteria were adults patients (age over 15 years) diagnosed as non-traumatic SAH; no definite abnormality of intradural vascular structures under baseline 3D-DSA except: vasospasm; available data on clinical and radiographic follow-up.

Results: During the study period, there were 252 patients diagnosed with SAH who underwent 3D-DSA. Of those, 42 patients (16.6%) had negative results of baseline 3D-DSA. Only 22 patients (52.4%) had available follow-up clinical data. At 6-month of follow-up, the numbers of patients with a modified Rankin Scale of 0 to 1 was 86.4% (19 patient). In total of 42 patients, 32 patients (76.2%) had the good prognosis. None of the 22 patients had no vascular aneurysm on follow-up MRA or CTA.

Conclusion: Angiogram-negative non-traumatic SAH was found 16.6% in northeast Thailand. Most patients had better prognosis (76.2%) and had negative results on follow-up radiological studies.

Keywords: Prognosis, Aneurysm, Digital subtraction angiography

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Non-traumatic subarachnoid hemorrhage [SAH] is a serious neurological condition and mostly caused by a ruptured intracnial aneurysm[(1)]. It defined as an extravasation of blood into the subarachnoid space between the pia and arachnoid membranes. It can be confirmed by a computed tomography [CT] or a magnetic resonance imaging [MRI] with fluid-attenuated inversion recovery [FLAIR] technique[(1)]. A conventional or three dimension [3D] digital subtraction angiography [DSA] is a gold standard radiographic modality to detect intracranial aneurysm[(1)]. Approximately, 15% of non-traumatic SAH have unknown cause of SAH or called angiogram-negative non-traumatic SAH[(1-3)]. In northeast Thailand, the prevalence of angiogram-negative non-traumatic SAH was even higher at 26.3%[(4,5)].

It is still debating if patients with angiogram-negative non-traumatic SAH should be further worked up[(6-8)]. Forster et al found that the false negative of initial DSA was quite low at 2%. And, the DSA is an invasive technique with a complication rate of 1.8%[(9)]. Further or repeating angiography may not be useful[(6)]. While, the other two studies suggested to perform a repeating angiography in non-perimesencephalic non-aneurysmal SAH to reduce morbidity and mortality[(7,8)]. One possible solution for this issue is to

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investigate a natural history of patients with angiogram-negative non-traumatic SAH. This study reviewed clinical course of angiogram-negative non-traumatic SAH patients in the 3D-DSA era.

Materials and Methods

This study was a descriptive retrospective study and conducted at Srinagarind Hospital or Khon Kaen University Hospital. The study period was between January 2014 and June 2016. The inclusion criteria were adults patients (age over 15 years) diagnosed as non-traumatic SAH by cranial non-contrast computed tomography [NCCT] or fluid-attenuated inversion recovery [FLAIR] image on magnetic resonance imaging [MRI]; no definite abnormality of intradural vascular structures under baseline 3D-DSA except: vasospasm; available data on clinical and radiographic follow-up.

Charts and radiographic findings of all eligible patients were reviewed. Baseline demographic data, co-morbid diseases, and risk factors of bleeding including previous history of SAH, family history of SAH, and antiplatelet/anticoagulant use were recorded.

Imaging technique

The present study reviewed baseline proven SAH on initial CT or MRI, diagnostic 3D-DSA and non-invasive follow-up imaging of CT Angiography [CTA] or magnetic resonance angiography [MRA]. All imaging studies were reviewed independently by two experienced neurointerventionists (one has 6-year experience and another one has 6-month experience). Unanimous definite interpretations were achieved.

Presence of subarachnoid hemorrhage on initial images was described in perimesencephalic pattern and non-perimesencephalic pattern. Perimesencephalic pattern was defined by 1) Central hemorrhage located immediately in front of the midbrain or within perimesencephalic, prepontine or medullary cisterns, 2) Absence of intraparenchymal bleeding, 3) Extension of blood into the proximal sylvian fissure with no more than a minute amount of blood in the lateral sylvian fissure, 4) Extension of blood without complete filling of the anterior interhemispheric fissure, 5) Absence of a frank intraventricular hemorrhage; sediment of a small amount of intraventricular blood is allowed[10]. Diffuse or cortical SAH and SAH with intraparenchymal hemorrhage or intraventricular hemorrhage are defined as non-perimesencephalic pattern.

Fisher scale for scoring SAH was used to determine the amount of SAH[11]. There were grade 0 to 4 representing unruptured to Intracranial or intraventricular clot with diffuse or no SAH. Hydrocephalus with or without extraventricular drainage was also recorded.

Diagnostic 3D-DSA was performed on a biplane neuroangiographic unit (Siemens Artis Zee Biplane). The DSA was conducted with a 1,024x1,024 matrix with a 17- to 20-cm FOV and injection of 16-mL contrast material in the internal carotid and vertebral arteries in 2 projections. Image data was sent to Picture Archiving and Communication System [PACS]. A complete cerebral 3DRA was carried out on biplane system with an 8-second 180 degree rotational run, with acquisition of 200 images and injection of about 2.5 mL contrast material per second in the internal carotid or vertebral arteries.

Non-invasive follow-up study of cranial CTA or MRA was performed approximately in 3 months after baseline 3D-DSA. CTA was performed on 64-slice multidetector row spiral CT scanner (SIEMENS, Somatom Definition Flash). Scan parameters were: 120 kV, 200 mAs, 0.6 mm slice thickness reconstruction was used. A nonionic iodinated contrast medium was administered 50 to 60 ml at 4 ml/s of injection rate, followed by flush of 30 ml isotonic saline at same injection rate. The direction of scanning was from aortic arch to the vertex. Bony structures were subtracted. Non-contrasted images and delayed images were also obtained.

MRA was performed on a 3 Tesla Philips (Achieva 3.0TX) using head coil. Scan parameters of Time of Flight image [TOF] were: TR 20/TE 3.5 ms, flip angle 20, field of view 220x198 mm in APxRL, matrix 400x249, slice thickness 0.6 mm axial orientation. Scan parameters of Contrast-Enhanced MRA were: TR 3.6/TE 1.22 ms, flip angle 25, field of view 320x280 mm in FHxRL, matrix 456x351, slice thickness 1 mm coronal orientation. Contrast material used was Gadovist® (gadobutrol) given intravenously of 1.0 mmol/ml (0.1 ml/kg) and followed by flush of 25 to 30 ml isotonic saline at 2 ml/s of injection rate.

Clinical status data

Clinical manifestation and severity at time of diagnosis was recorded using Hunt and Hess scale[12]. The follow-up clinical status was performed by using a modified Rankin Scale or mRS[13] at the maximum of one year after the diagnosis of SAH. The follow-up clinical data was also performed in those who were lost to follow-up by phone.

Statistical analysis

Descriptive statistics were used to calculate means or proportions. Cohen's Kappa statistic was also calculated for inter-observer agreement. Statistical analysis was performed by STATA/MP software version 13.0.

Results

During the study period, there were 252 patients diagnosed with SAH who underwent 3D-DSA. Of those, 42 patients (16.6%) had negative results of baseline 3D-DSA. Only 22 patients (52.4%) included in the present study. The mean age of all eligible patients was 55.8 years with a range of 31 to 74 years. A male: female ratio was 1.2: 1 (12 male and 10 female patients). Nine patients had co-morbid diseases including hypertension (6 patients; 27.3%) and diabetes (3 patients; 13.6%). No medication used such as aspirin or anticoagulant was reported in all patients.

Most patients had baseline Hunt and Hess clinical grading of 1 to 3 for 18 patients (81.8%) and 19 patients (86.3%) had non-perimesencephalic pattern as shown in Table 1. Among non-perimesencephalic pattern group, 15 patients had SAH with intraventricular hemorrhage, three patients had diffuse pattern of SAH without intraventricular hemorrhage or intraparenchymal hemorrhage, and one patient had SAH with both intraventricular hemorrhage and intraparenchymal hemorrhage. All patients were classified amount of SAH as III-IV using Fisher scale for SAH. All patients of perimesencephalic group had Fisher scale 3. Among 19 patients of non-perimesencephalic group, fifteen (15/19, 78.9%) were classified as Fisher scale 3 and the rest (4/19, 21.1%) were as Fisher scale 4. Eight patients (8/22, 36.4%) developed hydrocephalus. One of them (1/8, 12.5%) was perimesencephalic SAH. Seven patients (7/8, 87.5%) with non-perimesencephalic pattern developed hydrocephalus and two of them had been received extraventricular drainage treatment. Both patients had diffuse SAH with intraventricular hemorrhage.

3D-DSA imaging results

Data from 3D-DSA were reviewed by two experienced neurointerventionists. There were two imaging studies that had discordant results on distinguishing between infundibulum and true posterior communicating artery aneurysm. The final consensus was that all twenty-two patients had negative findings on 3D-DSA (90.91% Cohen's Kappa value). There was one patient who identified as having cerebral vasospasm (1/22, 4.5%). No procedural complication of 3D-DSA was occurred.

Follow-up imaging results

At approximately 3 months, CTA or MRA was performed in all 22 patients. None was detected any aneurysm. Three patients still had hydrocephalus. There were three patients (13.6%) developed cerebral infarction; one patient had evidence of vasospasm on baseline 3D-DSA.

Follow-up clinical status results

At 1-month of follow-up, the majority of patients (18/22, 81.8%) had mRS of 0 to 1. At 6-month of follow-up, the numbers of patients with mRS of 0 to 1 was 86.4% (19 patient) as shown in Table 2. All three patients with perimesencephalic pattern has mRS less than 2. At one year follow-up, 20 out of 22 patients had clinical evaluation. Of those, one patient with the non-perimesencephalic pattern and hydrocephalus died from pneumonia. Prior to pneumonia occurrence, the patient status was bed ridden and on extraventricular drainage. On the follow-up MRA, there was no vascular lesion but cerebral infarction at both frontal lobes were

Table 1. Hunt and Hess clinical grading and pattern of angiogram-negative non-traumatic subarachnoid hemorrhage

Grade	Perimesencephalic pattern n = 3	Non-perimesencephalic pattern n = 19	Total n = 22
Grade 1	-	-	-
Grade 2	1 (33.3)	6 (31.5)	7 (31.8%)
Grade 3	2 (66.7)	9 (47.4)	11 (50%)
Grade 4	-	3 (15.8)	3 (13.6%)
Grade 5	-	1 (5.3)	1 (4.6%)

Data presented as number (percentage)

Table 2. A modified Rankin Scale (mRS) within 6-month follow-up and pattern of subarachnoid hemorrhage

mRS	Perimesencephalic pattern n = 3	Non-perimesencephalic pattern n = 19	Total n = 22
Grade 0	2 (66.7)	11 (57.9)	13 (59.1)
Grade 1	1 (33.3)	5 (26.2)	6 (27.3)
Grade 2	-	1 (5.3)	1 (4.5)
Grade 3	-	1 (5.3)	1 (4.5)
Grade 4	-	1 (5.3)	1 (4.5)
Grade 5	-	-	
Grade 6	-	-	

Data presented as number (percentage)

detected. Note that this patient also had vasospasm on 3D-DSA.

Clinical status of the 20 patients who had negative baseline 3D-DSA and had been excluded from this study was retrieved by telephone. The majority of patients (13 patients; 65.0%) had mRS of 0 to 1. The other three patients (3/20, 15%) died from sequel of serious neurological complication, while four patients (4/20, 20%) were unable to contact.

Discussion

Approximately 8.6 to 15% of patients with non-traumatic SAH were angiogram-negative by the DSA. The incidence of angiogram-negative non-traumatic SAH was reduced by almost 50% by using the 3D-DSA; 8.6% to 4.2%[14] due to better quality of DSA technique. Similarly, the angiogram-negative non-traumatic SAH in our hospital was also reduced from 26.3% to 16.6%[4]. There is unclear why our number was quite higher than the previous report from Japan. The possible explanations for higher rates of angiogram-negative non-traumatic SAH than Japan in our setting reported in 2012[4] and also this study were causes and characteristics of patients. *Gnathostoma spinigerum* is one possible cause of angiogram-negative non-traumatic SAH in Thailand[15]. And, hypertension was the most common co-morbid disease in our patients (27.3%). As reported by the JNC7, hypertension is a major risk factor for hemorrhagic stroke[16]. Hypertension may cause micro-aneurysms which may not be detectable by the 3D-DSA[17]. Additionally, smaller study sample size than the study from Japan may be another possible reason (42 vs. 247 patients)[14].

Regarding characteristics of angiogram-negative non-traumatic SAH in this study, most patients (18 patients or 81.8%) presented with good Hunt and Hess clinical grading (I-III) even all patients had large amount of blood or Fisher scale of 3 to 4 by CT or MRI (Table 1). These results implied that clinical status may not be related to severity of SAH by radiographic findings in angiogram-negative non-traumatic SAH patients. Most of our patients (19/22, 86.3%) were classified as non-perimesencephalic pattern. These data were different from previous studies which had more prevalence on non-perimesencephalic pattern[3,7,8,18,19]. Note that all of our patients performed the diagnostic CT or MRI within three days of symptoms as the standard practice[20]. Fontanella et al reported that hydrocephalus was complication that commonly found in diffuse SAH more than in perimesencephalic SAH (6/6, 100%)[19]. That seemed similar to the present study, seven from eight patients (7/8, 87.5%) who had hydrocephalus were non-perimesencephalic group and two patients were performed extraventricular drainage.

The prognosis of angiogram-negative non-traumatic SAH patients were quite well. Most patients (86.4%) had good functional status of mRS less than 1 at six months. In total of 42 patients, the good prognosis was slightly lower to 76.2% (32 patients) in the worst case scenario. More specifically, those with perimesencephalic pattern seemed to have better prognosis than non-perimesencephalic pattern. Note that very few patients with perimesencephalic pattern (Table 2). One patient who died with aspirate pneumonia was a severe case. The poor clinical setting was non-perimesencephalic pattern and hydrocephalus development. Later on, cerebral infarction was occurred which may cause by cerebral vasospasm.

There were some limitations in the present study. First, this was a single site study in a university or referral center. This issue may be beneficial as well. Most SAH patients were likely to be referred to our center. Second, the sample size was quite small. Finally,

both MRA and CTA for follow-up investigations may not sensitive for small aneurysm detection.

In conclusion, angiogram-negative non-traumatic SAH was found 16.6% in northeast Thailand. Most patients had good prognosis (76.2%) and had negative results on follow-up radiological studies. Clinical prognostic factors may include non-perimesencephalic pattern, hydrocephalus, or vasospasm.

What is already known on this topic?

Approximately 8.6 to 15% of patients with non-traumatic SAH were angiogram-negative by the DSA.

What this study adds?

An angiogram-negative non-traumatic SAH was found 16.6% in northeast Thailand. This condition had good prognosis after one year of follow-up. Using CTA or MRA for further evaluation may not detect any vascular aneurysm.

Potential conflicts of interest

The authors declare no conflict of interest.

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