Secondary infarction in single or in multiple vascular territories: two different entities following subarachnoid hemorrhage?

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Abstract The pathogenesis of secondary infarctions (SI) after aneurysmal subarachnoid hemorrhage (SAH) is poorly understood. To assess whether SI in single (SSI) or multiple (MSI) vascular territories represent different disease entities, we compared clinical profiles of patients with these patterns of SI. CT/MRI-examinations of 448 patients were reviewed for new infarctions within 28 days after SAH, and categorized into SSI or MSI. Only patients with adequate follow-up imaging excluding any new infarctions were included for analysis (269 patients). Procedure-related infarctions were excluded. Odds ratios (ORs) with corresponding 95% confidence intervals (CI) were calculated for patients with SSI or MSI versus patients without SI to analyze differences in demographic characteristics, vascular risk factors, disease-related characteristics and treatment modalities. Thirty-six patients had SSI, 53 MSI and 180 no SI. ORs in MSI-patients were >1.5 times higher compared with ORs in SSI-patients for multiple vascular risk factors [MSI:5.4 (2.3–13) versus SSI:1.2 (0.5–2.8)], poor clinical condition on admission [MSI:4.6 (2.4–8.9) versus SSI:2.4 (1.1–5.2)], initial loss of consciousness [MSI:2.6 (1.3–5.3) versus SSI:1.1 (0.5–2.3)] and large

amounts of intraventricular blood [MSI:2.9 (1.4–5.8) versus SSI:1.5 (0.7–3.2)]. In multivariate analysis ORs remained higher in MSI for presence of multiple vascular risk factors [MSI:1.9 (1.2–2.9) versus SSI:1.1 (0.8–1.7)] and initial loss of consciousness [MSI:3.0 (1.0–8.9) versus SSI:1.6 (0.6–4.0)]. Our findings suggest that SSI and MSI after SAH are not distinct disease entities. MSI was related to the same characteristics as SSI but to a larger extent, specifically to the presence of multiple vascular risk factors, initial loss of consciousness, larger amounts of intraventricular blood, and poor clinical status on admission.

Keywords Delayed cerebral ischemia · Secondary infarction · Subarachnoid hemorrhage

Introduction

Delayed cerebral ischemia (DCI) is a major cause of poor outcome after subarachnoid hemorrhage (SAH). Although cerebral vasospasm has been indicated as the main cause of DCI [13], vasospasm and DCI do not always go hand in hand, which shows that vasospasm is not the only or essential factor for the development of DCI [2, 3, 9]. Other factors that may contribute to DCI besides large vessel vasospasm are inflammatory processes, intracranial microthrombosis, cortical spreading depolarisations and impaired cerebral autoregulation [4, 8, 14].

DCI may have several patterns. From a subdivision based on number and sites of infarctions on cerebral computed tomographic (CT) scans after SAH, two common patterns were distinguished [10]. These two common patterns were on the one hand a single cortical infarct and on the other multiple cortical and/or deep cerebral infarcts. It is unclear whether these secondary infarct (SI) patterns

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represent pathophysiologically different disease entities or different degrees of severity of the same vascular process.

We assessed whether secondary infarctions in single (SSI) or multiple (MSI) vascular territories represent different disease entities by comparing the clinical profiles of the patients with SSI or MSI with those of patients without infarction. We analyzed demographic characteristics, vascular risk factors, disease specific characteristics, and treatment modalities as determinants for development of SI.

Methods

Patients and data

From the prospectively collected database of all consecutive patients with SAH admitted to the University Medical Center Utrecht, we included all patients with an aneurysmal SAH who were admitted within 3 days after onset between January 1999 and June 2007. The diagnosis of SAH was based on a positive CT scan or xanthochromia of the cerebrospinal fluid. Presence of an aneurysm had to be confirmed by means of CT, MR or catheter angiography. For inclusion in the current study at least one follow-up scan, performed more than 24 h after the initial CT scan, was required.

For every patient we recorded data on gender, age, current smoking, history of hypertension, previous cardiovascular events (including stroke, myocardial infarction and peripheral vascular disease), hypercholesterolemia, diabetes mellitus, family history of cardiovascular events, and use of salicylic acid and statins at the time of admission. The clinical condition on admission was assessed with the World Federation of Neurological Surgeons scale and dichotomized in good (WFNS I to III) or poor (IV or V) [1]. We also recorded loss of consciousness at onset, and modality and timing of intervention. All patients were treated according to our standard protocol, including absolute bed rest, compressive stockings, intensive monitoring on our medium or intensive care unit until aneurysm treatment, nimodipine 360 mg daily orally, and intravenous administration of fluids aiming at normovolemia for 3 weeks.

Initial CT scans were evaluated for amount of blood, hydrocephalus and pre-existing infarction. The amount of cisternal and ventricular blood was assessed according to the method described by Hijdra et al. [7] and dichotomized at their median values. The presence of acute hydrocephalus was quantified and adjusted for age by means of the bicaudate index (BCI) divided by the corresponding upper limit per age group [6]. Acute hydrocephalus was defined as an age-adjusted relative BCI of >1 .

Follow-up scans were evaluated for new ischemic lesions. Lesions caused by extraventricular drains, pre-existing infarcts and hypodensities around a hematoma or in the vicinity of the operation area were not considered new infarctions. Only infarctions unrelated to angiography or aneurysm treatment were defined as “spontaneous infarction”. Infarctions were considered to be related to treatment if new neurological symptoms occurred directly after aneurysm treatment, and an infarct was visible in the territory of the parent vessel of the aneurysm on CT within 48 h after treatment. In case the time of development of infarction was uncertain (for example if a new infarction was present on CT >48 h after treatment and/or the neurological state of the patient directly after treatment could not be assessed due to sedative medication), an expert opinion was made by two of the authors, who were not aware of the risk factor profile. In this expert opinion the report of the operation or endovascular treatment was taken into account. In case of disagreement, the infarction was not counted as spontaneous infarction. To investigate if differentiation between edema and infarction could reliably be made in the presence of an intracerebral hematoma (ICH), we performed an interobserver study between three observers (two senior neurologists and one senior radiologist) in 25 patients with an additional ICH and a surrounding hypodensity. This study showed a large interobserver variability with kappa values around 0.50 (95%CI 0.06–0.96). Since subdivision in SSI and MSI in these cases could not reliably be made, patients with an ICH and a surrounding hypodensity were excluded.

The location(s) of spontaneous infarctions were determined by using validated arterial territory maps [11, 12]. We only included infarctions that developed within 28 days after SAH and were confirmed on a late follow-up scan. SSI was defined as infarction in one arterial territory and MSI as infarctions in more than one territory. Adequate follow-up (late CT or MRI follow-up between 28 days and 6 months after SAH) is necessary because within the first 28 days SSI could develop into MSI, and MSI could develop into SSI or MSI. Because new (silent) infarctions in other territories had to be excluded for a valid subdivision, we excluded patients with a single infarction or without any infarction who had no late follow-up scan.

All scans were reviewed for presence or absence of hypodensities by one author (NKdR). The first 35 scans were also reviewed independently by a senior vascular neurologist (CJMF). No disagreement was noticed with respect to presence or absence of hypodensities. All scans with hypodensities were independently reviewed and subdivided into SSI and MSI by NKdR and CJMF. In case of disagreement, consensus was reached in a meeting of all authors, including another senior vascular neurologist and a senior radiologist.

Data analysis

All patients with adequate radiological follow-up (SSI, MSI and NSI) were included for analysis. Odds ratios (ORs) for MSI or SSI compared with NSI were calculated with corresponding 95% confidence intervals (CI) using univariate logistic regression. We decided to perform an indirect comparison between MSI and SSI as primary analysis to increase the statistical power of the study. Furthermore, an indirect comparison reveals both the relative differences in ORs between MSI and SSI, and the absolute ORs for MSI and SSI separately. Additionally, we performed a direct comparison. All patient specific risk factors and disease specific characteristics were analyzed, except for the risk factors found in less than 10% of the patients. The total number of the vascular risk factors was analyzed as well: age above the median value, male gender, hypertension, previous cardiovascular disease, positive family history of vascular disease and current smoking. We defined high number of vascular risk factors as any number above the median number. Multivariate logistic regression was performed with all variables of which the association with MSI was more than 1.5 times higher or lower than the association with SSI.

Results

Of 828 consecutive patients with aneurysmal SAH admitted to our hospital within 3 days after onset of the

hemorrhage during the study period, we excluded 222 patients with incomplete scans. In 182 of these 222 patients no follow-up scan was made because of good outcome ($n = 65$), transfer to another hospital ($n = 7$), or early death ($n = 110$), and in 40 patients the initial or follow-up CT scan could not be retrieved. We excluded 149 patients because a large ICH with a surrounding hypodensity was present and subdivision in SSI and MSI could not reliably be made. Nine patients, in whom no consensus for presence or timing of infarction could be reached, were also excluded. An infarction related to treatment was recorded in 76 patients (17%). Eighty-nine of the 269 included patients with adequate follow-up developed spontaneous infarctions: 36 patients in a single vascular territory and 53 patients in multiple territories. In 180 patients no infarction was present (Fig. 1).

Baseline characteristics of these 269 patients are presented in Table 1. The median number of vascular risk factors was two. History of hypercholesterolemia, diabetes mellitus, use of salicylic acid and use of statins were recorded in less than 10% of patients, and were not used in the analyses.

Results of the indirect comparison (patients with MSI or SSI vs. NSI) are shown in Table 2. ORs were ≥ 1.5 for both MSI and SSI in five characteristics: positive family history of cardiovascular events, smoking, poor WFNS, and high amount of both cisternal and ventricular blood. The association with MSI was more than 1.5 times stronger than with SSI in eight characteristics: male gender, high age, history of cardiovascular events,

Fig. 1 Selection of patients with spontaneous single and multiple secondary infarction (SI) within 28 days after subarachnoid hemorrhage (SAH). *All treatment related infarctions were excluded. Depending on the presence or absence of other infarctions these patients were included in the SSI, MSI or the NSI group. †All gray marked patients had adequate radiological follow-up (late follow-up scan between 28 days and 6 months after onset of the SAH) and were included for analyses. SSI and NSI were defined as probable if there was no late CT or MRI follow-up to exclude new infarctions in other territories

Table 1 Baseline characteristics of 269 included patients

	Number of patients ^a	No secondary infarction (<i>N</i> = 180)	Single secondary infarction (<i>N</i> = 36)	Multiple secondary infarction (<i>N</i> = 53)
Patient characteristics				
Women (%)	269	129 (72)	26 (72)	33 (62)
Median age in years (range)	269	54 (18–83)	51 (26–76)	54 (29–77)
Hypertension (%)	263	43 (24)	8 (30)	14 (29)
History of cardiovascular events (%)	264	26 (15)	3 (9)	8 (16)
Family history of cardiovascular disease (%) ^b	269	26 (14)	9 (25)	9 (17)
Diabetes (%)	263	9 (5)	0 (0)	3 (6)
Hypercholesterolemia (%) ^b	269	7 (4)	3 (8)	3 (6)
Current smoking (%)	204	80 (54)	20 (67)	18 (67)
Use of salicylic acid (%)	247	12 (7)	5 (15)	6 (14)
Use of statins (%)	259	13 (7)	3 (8)	4 (9)
SAH characteristics				
Poor WFNS (IV, V) on admission (%)	268	37 (21)	14 (39)	29 (55)
Any loss of consciousness at onset (%)	239	61 (37)	12 (39)	27 (61)
Median amount of blood on initial CT				
Cisternal blood (range 0–30)	163	24 (0–30)	26 (0–30)	26 (0–30)
Intraventricular blood (0–12)	141	2 (0–12)	2 (0–8)	3.5 (0–12)
Acute hydrocephalus ^c (%)		49 (41)	15 (50)	22 (50)
External ventricular drainage	261	56 (33)	16 (44)	19 (36)
Site of the aneurysm (%)				
Posterior communicating artery	269	35 (19)	10 (28)	13 (25)
Internal carotid artery		6 (3)	1 (3)	5 (10)
Middle cerebral artery		23 (13)	9 (25)	4 (8)
Anterior communicating artery		77 (43)	9 (25)	20 (38)
Pericallosal artery		9 (5)	0 (0)	1 (2)
Basilar artery		13 (7)	3 (8)	2 (4)
Vertebral artery		12 (7)	1 (3)	4 (8)
Other		5 (3)	3 (8)	4 (8)
Treatment of the aneurysm (%)				
No treatment	269	4 (2)	0 (0)	19 (36)
Coiling	23	75 (42)	16 (44)	17 (32)
Clipping	108	101 (56)	20 (56)	17 (32)
Poor Outcome (GOS 1 or 2) at discharge (%)	138	2 (1)	2 (6)	28 (60)

WFNS World Federation of Neurological Surgeons Scale, GOS Glasgow Outcome Scale

^a Number of patients is <269 in case of unknown data

^b These risk factors were recorded as present if they were mentioned as present in patient's history, otherwise as absent or unknown

^c Acute hydrocephalus was defined as an age-adjusted relative BCI of >1

presence of >2 vascular risk factors (including these former three variables), poor WFNS, initial loss of consciousness and high amount of ventricular blood. There were no factors of which the association with SSI was more than 1.5 times stronger than with MSI. In the multivariate analysis the association with MSI remained statistically significant for initial loss of consciousness (OR 3.0; 95% CI 1.0–8.9) and presence of >2 vascular risk factors (OR 1.9; 1.2–2.9) (Table 3).

In the direct comparison (MSI vs. SSI) we found essentially the same associations, however with wider 95% CIs because of the smaller numbers of patients. Two associations reached statistical significance in the univariate analysis: presence of >2 vascular risk factors (OR 4.7; 1.5–14) and any loss of consciousness at onset (OR 2.5; 1.0–6.5). In the multivariate analysis of the direct comparison the presence of >2 vascular risk factors remained significantly associated with MSI (OR 1.8; 1.0–3.1).

Table 2 Differences in clinical and radiological data between patients with single and multiple secondary infarctions (SI) compared with patients without SI

	Number of patients	OR (95% CI) single SI (<i>n</i> = 36) vs. no SI (<i>n</i> = 180)	OR (95% CI) multiple SI (<i>n</i> = 53) vs. no SI (<i>n</i> = 180)
Patient characteristics			
Male gender	269	1.0 (0.4–2.2)	1.5 (0.8–2.9)
Age ≥ 54 years (median)	269	0.5 (0.2–1.1)	1.0 (0.6–1.9)
History of cardiovascular disease	264	0.5 (0.2–1.9)	1.1 (0.5–2.7)
History of hypertension	263	0.9 (0.4–2.2)	1.3 (0.6–2.6)
Family history of cardiovascular events	269	2.0 (0.8–4.7)	1.5 (0.9–2.5)
Current Smoking	204	1.7 (0.7–3.8)	1.7 (0.7–4.0)
More than two vascular risk factors ^{a,b}	203	1.2 (0.5–2.8)	5.4 (2.3–13)
SAH characteristics			
Poor WFNS (IV or V) ^b	268	2.4 (1.1–5.2)	4.6 (2.4–8.9)
Any loss of consciousness at onset ^b	239	1.1 (0.5–2.3)	2.6 (1.3–5.3)
Amount of cisternal blood ≥ 25 (median)	224	2.1 (1.0–4.5)	1.5 (0.8–2.9)
Amount of ventricular blood ≥ 2 (median) ^b	219	1.5 (0.7–3.2)	2.9 (1.4–5.8)
Acute hydrocephalus	194	1.4 (0.6–3.2)	1.4 (0.7–2.9)
External ventricular drainage	261	1.7 (0.8–3.4)	1.2 (0.6–2.2)
Clipping vs. coiling of the aneurysm	246	0.9 (0.5–1.9)	0.7 (0.4–1.6)

^a Number of following six risk factors: age above the median value, male gender, hypertension, previous cardiovascular disease, positive family history of vascular disease and current smoking. High number of vascular risk factors was defined as any number above the median (two)

^b Factors in multivariate analyses

WFNS World Federation of Neurological Surgeons Scale

Table 3 Multivariate analysis of associations of patients' and SAH characteristics with single or multiple secondary infarctions (SI) compared with patients without SI

	Number of patients	OR (95% CI) single SI (<i>n</i> = 36) vs. no SI (<i>n</i> = 180)	OR (95% CI) multiple SI (<i>n</i> = 53) vs. no SI (<i>n</i> = 180)
More than two vascular risk factors ^a	203	1.1 (0.8–1.7)	1.9 (1.2–2.9)
Poor WFNS (IV or V)	268	2.1 (0.8–5.6)	1.8 (0.5–5.9)
Any loss of consciousness at onset	239	1.6 (0.6–4.0)	3.0 (1.0–8.9)
Amount of ventricular blood ≥ 2 (median)	219	1.0 (0.8–1.2)	1.1 (0.9–1.3)

WFNS World Federation of Neurological Surgeons Scale

^a Number of the following six risk factors: age above the median value, male gender, hypertension, previous cardiovascular disease, positive family history of vascular disease and current smoking. High number of vascular risk factors was defined as any number above the median

Discussion

Our study showed that all patients with secondary infarction had a similar clinical profile. Both infarct patterns (single or multiple vascular territories) were related to characteristics representing poor initial condition after SAH and presence of vascular risk factors when compared with patients without infarction. However, patients with MSI had an obviously stronger association with these risk factors than patients with SSI, with odds ratios being higher for MSI than for SSI regarding the presence of multiple vascular risk factors, poor neurological condition on

admission, initial loss of consciousness, and large amounts of intraventricular blood. These results suggest that SSI and MSI after SAH are not distinct disease entities, but consequences of increasing severity of the same risk factors, and therefore different degrees of the same pathophysiological process.

A previous study distinguished five distribution patterns of infarctions after SAH (based on location and number of infarctions) and analyzed factors that determined their occurrence. The authors suggested that single cortical or multiple cortical and/or deep infarctions are two common types of SI, and may represent different pathophysiological

mechanisms [10]. That conclusion was based on associations of occurrence of multiple infarctions with history of diabetes, early hydrocephalus and requirement of external ventricular drainage (univariate analysis). Requirement of external ventricular drainage was the only independent predictor in their multivariate analysis. In contrast to our methods, this previous study investigated a small population of 56 patients, directly comparing patients with SI in single or multiple vascular territories, without excluding treatment related infarctions and with limited CT follow-up time. Trends found for associations of multiple infarctions with higher age, poor clinical condition on admission and presence of vascular risk factors corresponded with our findings. Because of the limited statistical power with 56 patients, relevant factors such as initial WFNS score may have been undetected. To reduce this risk of type II error, we made an indirect comparison that included 269 patients. In our study acute hydrocephalus was assessed as BCI adjusted for age, which we feel is a more accurate measure than BCI alone, and found no strong association between MSI and hydrocephalus. The factors that proved to be the most important determinants in our study (presence of initial loss of consciousness and presence of multiple vascular risk factors) were not studied in the previous study.

We studied a large population of 269 SAH patients, 89 of whom developed spontaneous infarctions after SAH. One of the strengths of our study is the meticulous elimination of possible sources of confounding data due to equivocal assessment of spontaneous SI. All CT scans were independently reviewed by two authors and a specialist team in case of disagreement. We performed an interobserver study of the assessment of hypodense lesions at the location of intracerebral hematomas. Because distinction between perihematomal edema and (hemorrhagic) infarction proved difficult to make, we excluded patients with ICH and surrounding hypodense lesions in the comparison between patients with SSI and MSI. For similar reasons we also excluded patients with hypodensities in the operation field. In a study on pathogenesis of DCI, it is essential to include only infarctions of which it is completely sure that they are unrelated to a procedure. For that reason we considered infarction as procedure related, if there was a chance, not only if it was proven to be procedure related. For analysis we included only patients with adequate radiological follow-up. The disadvantage of this elimination of several sources of bias is that we had to exclude large numbers of patients. However, because the original sample we studied was very large, we were still able to perform sound multivariate analyses.

As this was a retrospective study, we had some missing data on the characteristics studied. Also, there was no prospective protocol for standardized CT scanning at

predetermined time points and patients had scans at varying time points during their stay in our hospital. Since we analyzed two radiological patterns of SI, clinical symptoms of secondary ischemia without an infarct on CT or MRI were not taken into account. MRI was not performed in the acute phase of SI and was performed only in a minority of our patients for follow-up of endovascular treatment of the aneurysms. Follow-up by MRI was mainly performed in patients without infarction, and more in SSI than in MSI. Therefore, the fact that MRI is more sensitive is not likely to have biased our results.

Previous literature found that focal or diffuse distribution of vasospasm by TCD or angiogram failed to reliably predict the subsequent pattern of brain infarction [10]. The aim of our study was not to assess the relation between vasospasm and infarction, but to investigate the existence of two different entities of SI. We defined SI on non-contrast CT or MRI and had no full information on presence or absence of vasospasm in all patients. Though vasospasm may contribute to the development of SI, infarction and vasospasm do not always go hand in hand. Obviously, in observational studies SI is a more important outcome event than the presence of arterial spasm by angiography or TCD [5, 15]. Our data give no information whether generalized vasospasm was more present in patients with MSI, or focal vasospasm in patients with SSI. However, other authors found no differences in occurrence or extent of vasospasm in patients with different single or widespread infarct patterns [10]. Therefore, we feel that this is not an important shortcoming of our study.

In this study the presence of more than two vascular risk factors was associated with development of SI. We could not find previous studies with similar findings. Since the relationship between vascular risk factors and SI was not the primary aim of the current study, no definitive conclusions can be drawn from this finding. Future studies should focus on the identification of additional clinical risk factors of SI and unravel the association between vascular risk factors and SI after SAH. Identification of risk factors may improve our understanding of the pathogenesis of SI and help to tailor preventive treatment to the risk profile of individual patients.

In conclusion, our findings suggest that SSI and MSI do not represent two different disease entities. We found that MSI is related to the same characteristics as SSI but to a larger extent, specifically to presence of multiple vascular risk factors, initial loss of consciousness, larger amounts of intraventricular blood and poor clinical status on admission. Our results underline the importance of clinical risk factors for occurrence and extent of secondary infarction after SAH.

Conflict of interest None.

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