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Prognostic value of the 2010 consensus definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage

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ABSTRACT

Background and purpose: Delayed cerebral ischemia (DCI) complicates the recovery of approximately 30% of patients with aneurysmal subarachnoid hemorrhage (aSAH). The definition of DCI widely varies, even though a consensus definition has been recommended since 2010. This study aimed to evaluate the prognostic value of the 2010 consensus definition of DCI in a cohort of patients with aSAH.

Methods: We conducted a single-center, retrospective, observational study that included consecutive adult patients with aSAH who were admitted to the intensive care unit from January 2010 to December 2014. DCI was evaluated 48 h to 14 days after onset of aSAH symptoms using the 2010 consensus criteria and outcome was assessed by the Glasgow Outcome Scale (GOS) at discharge from hospital.

Results: A total of 340 patients were analyzed and the incidence of DCI was 37.1%. The median time from primary hemorrhage to the occurrence of DCI was 97 h. Neurological deterioration was observed in most (89.7%) of the patients who fulfilled the DCI criteria. The occurrence of DCI was strongly associated with an unfavorable outcome (GOS 1–3) at hospital discharge (OR 2.65, 95% CI 1.69–4.22, $p < 0.001$).

Conclusions: The incidence of DCI after aSAH is high and its occurrence is strongly associated with an unfavorable neurological outcome. This finding adds to the previous literature, which has shown that DCI appears to be a major contributor affecting the functional ability of survivors of aSAH. To further advance reliable knowledge of DCI, future studies should adhere to the consensus definition of DCI.

1. Introduction

Despite advances in neurocritical care, aneurysmal subarachnoid hemorrhage (aSAH) remains a devastating disease with a 1-year mortality rate up to 50% [1]. Additionally, many survivors of aSAH struggle with neurological and psychosocial impairment [2]. Only 25% of survivors report a complete recovery [3]. A major contributor to a poor outcome is delayed cerebral ischemia (DCI), which complicates recovery in approximately 30% patients with aSAH [4]. The typical risk period for DCI is 3–14 days after onset of aSAH [4,5]. In part, DCI is a continuum of pathophysiological mechanisms that are initiated during early brain injury, which is usually defined as injury in the first 72 h after aSAH [6–8]. The specific pathophysiology of DCI is still incompletely understood, but it appears to be multifactorial. Ischemia from vasospasm in cerebral arteries is one of the mechanisms that causes DCI, but contrary to historical dogma, it is not the sole contributory factor [5]. Patients can deteriorate neurologically because of DCI without angiographic vasospasm [9] and they can also have angiographic vasospasm without DCI [10]. Other biochemical processes that might be involved in DCI include blood–brain barrier disruption, cerebral microthrombi, oxidative stress, and inflammation [4,5,11].

The terminology used for DCI varies, which makes comparison of studies challenging [12,13]. Increasing knowledge of the pathophysiology of DCI requires validation and standardization of definitions and

Abbreviations: DCI, delayed cerebral ischemia; aSAH, aneurysmal subarachnoid hemorrhage; GOS, Glasgow Outcome Scale.

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terminology of DCI. To address this problem of heterogeneity of definitions, an international panel of experts in aSAH developed and proposed a definition of DCI to be used as an outcome measure in future clinical trials and observational studies [12]. A recent preprint of a systematic review indicated a steady increase in publications referring to the 2010 consensus definition of DCI. However, the majority of cohort studies and clinical trials omitted the consensus definition [14].

Therefore, this study aimed to evaluate the prognostic value of the 2010 consensus definition of DCI using a large cohort of patients with aSAH.

2. Methods

2.1. Study design

We conducted a single-center, retrospective, observational study. The local ethics committee of Pirkanmaa approved the study design (approval no. R115508S). No informed consent was required because the data were retrospectively obtained from medical records.

The study population consisted of consecutive adult patients with aSAH who were admitted to the intensive care unit (ICU) of Tampere University Hospital from January 2010 to December 2014. Tampere University Hospital is one of five tertiary referral centers in Finland serving a population of approximately 1 million inhabitants. All patients requiring neurointensive care in the catchment area of Tampere University Hospital are treated at the Tampere University Hospital intensive care unit. All aSAH patients admitted to the Tampere University Hospital, unless deemed moribund, are initially treated in the ICU.

2.1.1. Selection of patients

The onset of symptoms associated with aSAH was registered from the patients' records. We excluded patients with an unknown time of onset of symptoms and those whose admission was longer than 48 h after the onset of symptoms. Additionally, patients who were admitted to the ICU solely on the basis of organ donation, and moribund patients with unsecured aneurysms were excluded. All patients received neurointensive care in accordance with a standardized in-house protocol on the basis of international multidisciplinary consensus guidelines [15,16].

2.1.2. Assessment of DCI

DCI was evaluated independently by 3 of the investigators (AK, AV, and ER) from the ICU database (Centricity Critical Care Clinisoft; GE Healthcare, Barrington, IL, USA) and electronic medical records at 48 h to 14 days from the onset of aSAH symptoms using the criteria defined by Vergouwen et al. [12] In case of any doubt, all investigators thoroughly evaluated the patient's history and a consensus decision was made. Accordingly, DCI was defined as follows: neurological deterioration and a reduction in the Glasgow coma scale (GCS) score by $\geq$2 points, which was sustained for longer than 1 h (within a 4-h window), a new focal neurological deficit, which lasted longer than 1 h, or a new ischemic episode on neuroimaging data that was not related to the primary aSAH or neurosurgery. The specific criteria for DCI-related infarction on neuroradiological imaging are shown in Supplementary Table I. The exclusion criteria for DCI were based on a previous study that focused on the interrater agreement in the diagnosis of DCI [13] and were as follows: rebleeding, intracranial cerebral pressure repeatedly >20 mmHg, acute hydrocephalus, acute metabolic abnormality, new infection, a seizure confirmed on electroencephalogram, association with sedative medication, and causality related to a neurosurgical procedure within 24 h. The detailed exclusion criteria are shown in Supplementary Table II. These exclusion criteria were evaluated from the ICU database and medical records. The data in the ICU database is gathered in a prospective manner during patient care.

2.1.3. Assessment of other clinical factors and neurological outcome

We collected the following information from the neurosurgical aneurysm database: Glasgow Outcome Scale (GOS) score [17], aneurysm location, treatment modality, Hunt and Hess scale grade [18], and Fisher scale score [19].

Neurological outcome was assessed with the GOS at discharge from hospital. The neurological outcome was further dichotomized as favorable (GOS scores: 4–5) and unfavorable (GOS scores: 1–3). The severity of aSAH in an initial head computed tomographic scan was evaluated by a neurosurgeon with the Fisher scale and the severity of early brain injury at hospital admission was assessed with the Hunt and Hess grading scale. The Fisher scale was dichotomized as non-severe (Fisher scores: 1–2) and severe (Fisher scores: 3–4). The severity of early brain injury at admission was dichotomized as mild (Hunt and Hess grades: 1–3) and severe (Hunt and Hess grades: 4–5).

2.1.4. Statistical methods

Age was normally distributed in our study population. Therefore, the *t*-test was used to test differences in age between patients with and without DCI. The associations of categorical variables and DCI were evaluated using the Pearson chi-square test. Binary logistic regression was used to evaluate associations of categorical variables and age with unfavorable neurological outcome in univariate analysis. A multivariate logistic regression model was created to identify independent predictors of unfavorable neurological outcome. All statistical analyses were performed using R version 3.6.3 (The R Foundation, Vienna Austria).

3. Results

A total of 439 consecutive patients with aSAH who were admitted to the ICU were evaluated and 99 patients were excluded (Fig. 1). The characteristics of the remaining 340 patients are shown in Table 1. The

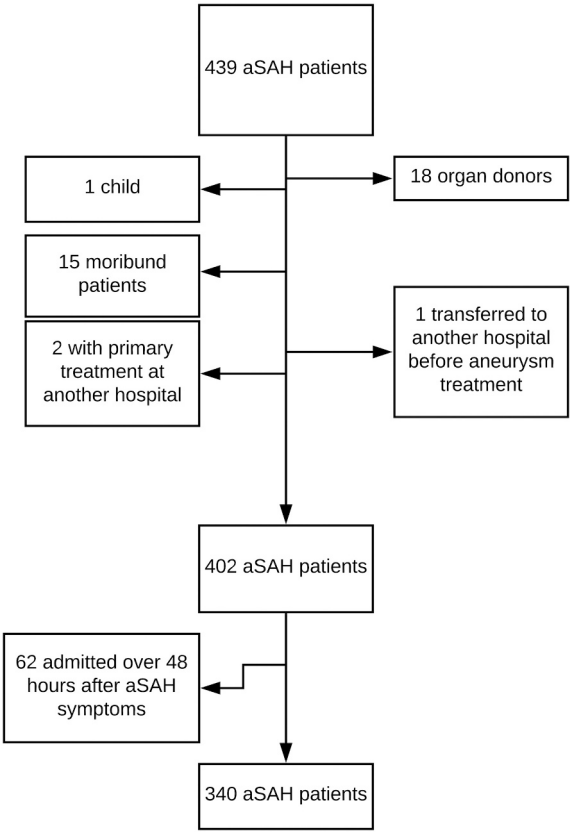

Fig. 1. Flowchart of the study.
A total of 439 consecutive patients with aSAH who were admitted to Tampere University Hospital intensive care unit between January 2010 and December 2014 were evaluated, and 99 patients were excluded.

Table 1
Demographics and baseline characteristics of the study population.

Variable	DCI (n = 126)	%	No DCI (n = 214)	%	p value
Mean age, years (± SD)	55.7 ± 12.7		56.8 ± 12.2		0.474
Sex					
Male	47	37.0	87	40.7	0.620
Female	79	62.7	127	59.3	
Aneurysm location					
Anterior circulation	105	83.3	170	79.4	0.460
Posterior circulation	21	16.7	44	20.6	
Treatment modality					
Endovascular treatment	69	54.8	113	52.8	0.813
Surgical clipping	57	45.2	101	47.2	
Hunt and Hess scale grade					
Non-severe (1–3)	80	63.5	150	70.1	0.256
Severe (4–5)	46	36.5	64	29.9	
Fisher scale score					
Non-severe (1–2)	6	4.8	20	9.3	0.185
Severe (3–4)	120	95.2	194	90.7	
Neurological outcome					
Unfavorable (GOS score: 1–3)	84	66.7	92	43.0	< 0.001
Favorable (GOS score: 4–5)	42	33.3	122	57.0	

Abbreviations: DCI, delayed cerebral ischemia; GOS, Glasgow Outcome Scale; SD, standard deviation.

majority (60.6%) of patients were women and the mean (SD) age was 56.4 ± 12.4 years. Ruptured anterior circulation aneurysms (80.9%) had a clear over-representation compared with posterior circulation aneurysms. Endovascular aneurysm occlusion (53.5%) was slightly more common than surgical clipping.

During the 14-day observational period, 126/340 (37.1%) patients met the DCI criteria as defined by the 2010 consensus definition. The median interval from the primary ictus to DCI was 97 h (interquartile range, 68–151 h). Neurological deterioration (i.e., decline in GCS score, new focal neurological deficit, or both) was observed in most of the patients (113/126, 89.7%). In 13 patients, fulfillment of the DCI criteria was based solely on neuroradiological imaging (Table 2). The Hunt and Hess scale grade, Fisher scale score, aneurysm location, treatment modality, and sex were not associated with fulfillment of the 2010 consensus DCI criteria (Table 1). The occurrence of DCI was strongly associated with an unfavorable neurological outcome at hospital discharge (OR 2.65, 95% CI 1.69–4.22, $p < 0.001$Table 3).

In univariate binary logistic regression analysis, DCI, age, the Fisher scale score, and the Hunt and Hess scale grade showed significant associations (all $p < 0.001$) with an unfavorable neurological outcome (Table 3). In multivariate analysis, these same variables were also independent risk factors (DCI, OR 3.23, CI 1.90–5.60; age[years], OR 1.06, CI 1.04–1.08; Fisher scale score, OR 4.4, CI 1.43–17.43; Hunt & Hess scale grade, OR 5.8, CI 3.30–10.59, all p < 0.001) for an unfavorable neurological outcome (Table 3).

Table 2
Description of the diagnosis for DCI and timing of each diagnosis in hours.

Criteria for DCI diagnosis (n = 126)	N	%	Median	IQR
Decline in GCS score alone	10	7.9	69.8	61.1–134.8
Focal deficit alone	12	9.5	117.4	104.1–132.4
Decline in GCS score and focal deficit	18	14.3	83.0	59.1–93.3
Decline in GCS score, focal deficit, and new infarction	30	23.8	94.4	63.9–146.1
Decline in GCS score and new infarction	18	14.3	84.0	59.2–96.7
Focal deficit and new infarction	25	19.8	118.0	77.0–165.2
New infarction alone	13	10.3	171.3	115.4–210.5

Abbreviations: DCI, delayed cerebral ischemia; GCS, Glasgow coma scale; IQR, Interquartile range.

4. Discussion

Our study evaluated the prognostic potential of the 2010 international panel of experts' consensus definition of DCI [12] in a large retrospective cohort of patients with aSAH. Fulfillment of the DCI criteria was a robust and independent risk factor for an unfavorable neurological outcome at discharge from hospital, as defined by GOS scores of 1 to 3. The median time from primary hemorrhage to occurrence of DCI was 97 h. Neurological deterioration was observed in most of the patients who fulfilled the DCI criteria (89.7%). Previously well-known independent risk factors for an unfavorable neurological outcome [20–23] such as the Hunt and Hess scale grade, the Fisher scale score, and increasing age, were also found in the current study.

In this study cohort, patients who met the 2010 consensus DCI criteria during the first 14 days after aSAH were prone to an unfavorable neurological outcome at discharge from hospital. Galea et al. [20] previously reported similar results from a large register-based study where DCI according to the 2010 consensus definition was an independent risk factor for poor neurological outcome at discharge from hospital. However, in contrast to the current study, they were unable to comprehensively examine the cases, and therefore, a detailed description of the diagnosis of DCI was missing. We extensively examined the cases for DCI inclusion and exclusion criteria from the ICU database, and in case of any lack of clarity regarding DCI, all investigators thoroughly evaluated the patient's history. Furthermore, we assessed the DCI criteria hourly from the ICU database, and therefore, the exact evolution of DCI was known.

The incidence of DCI in our cohort (37.1%) was high compared with the previous literature. In a systematic review that evaluated the association between radiological scales and the incidence of DCI, the incidence of DCI ranged from 11% to 57% in patients [24]. However, the most commonly reported incidence of DCI is approximately 30% [4,5]. Galea et al. [20] reported an incidence of 21.7% for DCI in their register-based study, which adhered to the 2010 consensus definition of DCI. A recent systematic review of outcome measures used in aSAH clinical research showed that there was substantial heterogeneity in the definition of DCI [25]. Only 40% of the studies described some form of clinical deterioration associated with DCI. Some of the studies that were included required a combination of clinical and radiological measures to fulfill DCI criteria, and others were purely clinical or radiological, and some did not provide a definition [25]. The relatively high incidence of DCI in the current study could reflect over-sensitivity of the 2010 consensus criteria.

Weir et al. [28] showed that the maximal angiographic vasospasm occurs 6 to 8 days after aSAH. That is significantly later than the fulfillment of DCI criteria in many patients in our study cohort, especially if the DCI diagnosis was based on or partly on the GCS score decline. Since the past literature has focused on the angiographic vasospasm it is possible that by adhering to the consensus 2010 DCI criteria the development of DCI can detected earlier than has been previously assumed.

Usually the assessment of new focal deficiencies in patients is simple, especially when focal deficiencies are clear (e.g. hemiparesis). However, if a patient is in a state of altered consciousness or is not cooperating, then assessment may be more complicated. Assessment of consciousness with the GCS score is prone to interrater variability [26] and the GCS score is unreliable with intubated patients [27]. Mild fluctuation of the GCS score is common after aSAH in the ICU environment (e.g., because of sleep deprivation and unexpected effects of analgo-sedative drugs). However, only 7.9% of the patients in our cohort fulfilled the DCI criteria solely on the basis of deterioration of the GCS score. Furthermore, the overall interrater agreement for the 2010 consensus definition of DCI was reported to be excellent when following explicit exclusion criteria [13], and this was also found in our study.

The 2010 consensus statement also recommends that neuroradiological imaging should be performed between 24 and 48 h after invasive

Table 3
Binary logistic regression for predicting an unfavorable neurological outcome.

	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
DCI						
yes	2.65	1.69–4.22	< 0.001	3.23	1.90–5.60	< 0.001
no	1			1		
Age (years)	1.06	1.04–1.08	< 0.001	1.06	1.04–1.08	< 0.001
Sex						
Male	1.26	0.81–1.95	0.304	1.65	0.98–2.83	0.063
Female	1			1		
Hunt and Hess scale grade						
4–5	6.46	3.83–11.26	< 0.001	5.8	3.30–10.59	< 0.001
1–3	1			1		
Fisher scale score						
3–4	6.66	2.48–23.17	< 0.001	4.4	1.43–17.43	< 0.001
1–2	1			1		
Aneurysm location						
Anterior circulation	1.13	0.66–1.95	0.650	1.33	0.70–2.56	0.387
Posterior circulation	1			1		
Treatment modality						
Endovascular	1.14	0.75–1.75	0.544	1.21	0.72–2.05	0.476
Surgical	1			1		

Abbreviations: CI, confidence interval; DCI, delayed cerebral ischemia; OR, odds ratio.

treatment of the aneurysm to rule out possible iatrogenic brain lesions [12]. In our study, neuroradiological imaging was performed when decided as clinically necessary. When neuroradiological imaging is not performed systematically, it can complicate assessment of etiology of the infarction if it is found at a later date. Additionally, even when using the strict criteria for infarction, which is attributed to DCI, ascertainment of cases can be ambiguous [13]. It may also be debated whether the appearance of a small infarction on neuroradiological imaging without any clinical symptoms associated with it is significant. Overall, because most of the past literature is based on variable definitions of DCI, whether this increased incidence reflects only our study cohort or whether an increased incidence of DCI will be observed in other studies complying with the consensus criteria of DCI remains speculative.

As expected in our study, high Hunt and Hess scale grades and high Fisher scale scores were prognostic for an unfavorable neurological outcome. Surprisingly, Hunt and Hess scale grades and Fisher scale scores were not associated with fulfillment of the 2010 consensus DCI criteria. A recent systematic review showed that the Fisher scale, modified Fisher scale, and Hijdra sum scores were associated with DCI [24]. However, most of the studies evaluated in this review did not adhere to the 2010 consensus definition of DCI. Therefore, the definition of DCI affects how it is associated with scales reflecting the severity of early brain injury (i.e., Hunt and Hess and Fisher scales). The Fisher scale was developed in the 1980s and it was used to predict angiographic vasospasm on the basis of the amount of blood visualized in an initial head computed tomographic scan [19]. Because the 2010 consensus definition of DCI does not require angiographic vasospasm as a DCI criterion, this might explain a weaker association between the Fisher scale score and DCI. The lack of association between fulfillment of DCI criteria and the Hunt and Hess scale grade might be caused by more simple recognition of DCI criteria in patients whose neurological status is not comatose from the onset of aSAH.

This study has some limitations. First, this was a retrospective, single-center study. This limits the generalizability of the results but reduces bias of differences in interpretation of DCI criteria and selection of patients. Second, because of the retrospective nature of the study, we were unable to include some of the known risk factors for DCI (e.g., smoking) in logistic regression analysis. The retrospective nature of this study also made the assessment of infarction etiology uncertain. Third, because the neuroradiological imaging was done solely on the basis of clinical need, the assessment of the etiology of infarction can be complicated and case ascertainment can be open to interpretations. Finally, the neurological outcome was only assessed at discharge from hospital. We acknowledge that this hinders conclusions about the long-term neurological outcome of patients.

The multifactorial pathophysiology of DCI causes further brain injury and impairs neurological recovery of survivors of aSAH [4]. In practice, in the clinic and in research, detecting patients suffering from DCI is often challenging. Highly variable use of DCI definitions and terminology in the previous literature obscures well-defined conclusions of the incidence of DCI and its associations with other clinical variables, such as neurological outcome [12,14]. An explicit consensus recommendation for the definition of DCI exists, but it is underutilized [12,14]. In future research, use of a uniform terminology and definition of DCI (i.e., 2010 consensus criteria) is essential to further advance understanding of the pathophysiology, incidence, and effect of DCI on neurological outcome of this extremely complex phenomenon.

5. Conclusions

Fulfillment of the 2010 consensus DCI criteria was high in this study cohort and it was an independent predictor of unfavorable neurological outcome at discharge from hospital. This finding adds to the previous literature where DCI appears to be a major contributor affecting the functional ability of survivors of aSAH. By adhering to a uniform terminology and definition of DCI, improving understanding of this extremely complex phenomenon should be possible, as well as possibly improving patients' outcomes in the future.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2020.117261.

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