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Mental versus physical fatigue after subarachnoid hemorrhage: differential associations with outcome

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Key words: subarachnoid hemorrhage, mental fatigue, physical fatigue, functional outcome, return to work

Abstract

Background: Fatigue is a major consequence of subarachnoid hemorrhage (SAH), but the specific characteristics are unclear. Our objective was to investigate the nature of post-SAH fatigue (mental or physical) and to determine the relationship with functional outcome in the chronic stage. Also, the possible influence of mood disorders and acute SAH-related factors (SAH type and external cerebrospinal fluid (CSF) drainage) on the presence of fatigue was investigated.

Methods: Patients with an aneurysmal SAH (aSAH) or angiographically negative SAH (anSAH) were assessed 3 to 10 years post-SAH (N = 221). Questionnaires were used to investigate mental and physical fatigue and mood. Functional outcome was examined with the Glasgow Outcome Scale Extended (GOSE). Between-group comparisons and binary logistic regression analysis were performed.

Results: Frequencies of mental and physical fatigue were 48.4% and 38.5% respectively, with prevalence of mental fatigue being significantly higher. A two-way ANOVA with SAH type and external CSF drainage as independent variables and mental fatigue as dependent variable, showed a significant main effect of CSF drainage only ($p < 0.001$). Only mental fatigue explained a significant part of the variance in long-term functional outcome (Model $\chi^2 = 52.99$, $p < 0.001$; Nagelkerke $R^2 = 0.32$).

Conclusions: Mental fatigue after SAH is a serious burden to the patient and is associated with impaired long-term functional outcome. Distinguishing different aspects of fatigue is relevant as mental post-SAH fatigue might be a target for treatment aimed to improve long-term outcome.

Fatigue is one of the major consequences after subarachnoid hemorrhage (SAH) [1,2], however, relatively little is known about the specific characteristics of post-SAH fatigue. Moreover, it is unknown whether fatigue is associated to long-term functional outcome, including return to work (RTW), following SAH.

After SAH, reported frequencies of fatigue vary from 31% to 90% [3–6], depending on the instrument used, timing post-SAH, and type of SAH [1]. Post-SAH fatigue is often investigated as a unitary construct, despite the fact that fatigue after brain injury is a multidimensional phenomenon, with physical and mental components [7,8]. Physical and mental fatigue are notably different in nature and manifestation, with mental fatigue being most typical for patients with brain injury [9,10]. Mental fatigue is described as a sustained feeling of exhaustion, lack of energy, and reduced initiative, resulting from performing mentally demanding activities, and accompanied by other symptoms such as stress sensitivity and irritability. In contrast, physical fatigue is generally characterized as physically felt exhaustion, with coexisting symptoms such as bodily pain [9,11,12]. Knowledge about the precise nature and characteristics of post-SAH fatigue is lacking, but may be paramount as different types of fatigue might require different treatments.

To understand the different aspects of post-SAH fatigue, it is also important to investigate possible comorbid variables. Anxiety and depression have been associated to post-SAH fatigue in general [4,6], however relationships between mood disorders and mental and physical fatigue separately have not been investigated until now. Furthermore, several acute SAH-related mechanisms could possibly be associated with long-term consequences. SAH most often results from rupture of an intracranial aneurysm (aneurysmal SAH [aSAH]), but in around 15% of cases no structural cause for the hemorrhage can be found (angiographically negative SAH [anSAH]). Generally, anSAH is regarded a benign pathology, but only one study compared levels of fatigue between aSAH and anSAH patients and found no differences in percentages of overall fatigue [13]. Also, external cerebrospinal fluid (CSF) drainage (for acute hydrocephalus and in cases with raised intracranial

pressure) is common after SAH and has been related to unfavorable long-term outcome [14,15].

However, the relation between CSF drainage and fatigue post-SAH is unknown.

Moreover, the possible relationship between specific aspects of post-SAH fatigue and functional outcome, including RTW, has barely been investigated. A few studies found associations between fatigue and Quality of Life [5,16] and leisure resumption after SAH [17]. In other subtypes of stroke, it is well established that fatigue affects RTW [18] and functional independence [19,20].

The aim of the present study is twofold. Firstly, to investigate whether mental and physical fatigue can be distinguished after SAH and to which extent both types are related to mood disorders and SAH-related variables. Secondly, to investigate the predictive value of mental and physical fatigue for long-term functional outcome.

Methods

Patients and procedure

Survivors after SAH treated at the University Medical Center Groningen (UMCG) between 2005 and 2012 were eligible for inclusion in the present study. SAH was diagnosed by computed tomography (CT). CT angiography and digital subtraction angiography were performed to determine the presence of a symptomatic intracranial aneurysm (aSAH) or to prove its absence (anSAH). Exclusion criteria were age under 18 years at the time of SAH or severe comorbidity that could interfere with the outcome of the study. Demographical data (age, sex), date of the SAH, clinical condition on admission (World Federation of Neurological Surgeons score), and presence of motor impairment (total or partial loss of a body function) were obtained from patients' medical reports. In aSAH patients, location of the symptomatic aneurysm, as well as treatment (coiling/clipping) were recorded. External CSF drainage (external ventricular [EVD] or external lumbar drainage [ELD]) was initiated for suspected increased intracranial pressure based on somnolence and/or the presence of severe headache, with or without enlarged ventricles on CT-scan. Persisting CSF resorption disturbances

(based on enlarged ventricular system on follow-up CT-scan and clinical signs/symptoms), were treated with ventriculo-peritoneal (VP) shunting.

All included patients had also participated in one of our two previous cohort studies: a retrospective study of long-term resumption of daily activities [17] and a prospective study of cognitive functioning post-SAH [21]. Questionnaires on fatigue and mood were sent to all patients between 3 to 10 years post-SAH followed by a structured telephonic interview about functional outcome, including RTW. The study was approved by the Medical Ethical Committee of the UMCG. All participants gave written informed consent and were treated in accordance with the Declaration of Helsinki.

Questionnaires

Fatigue. The Dutch Multifactor Fatigue Scale (DMFS[9]) is designed to measure fatigue in the chronic phase after acquired brain injury and consists of 38 items (scoring 1: totally disagree, to 5: totally agree). Higher scores indicate higher levels of fatigue. The DMFS is subdivided in five scales, the following two subscales were used in this study:

- Mental-f, addressing consequences and precursors of mental fatigue (range 7-35);
- Physical-f, addressing consequences and precursors of physical fatigue and physical fitness (range 6-30).

Scores on both subscales were examined in contrast to a norm group of 129 healthy control participants (without neurological conditions, psychiatric disorders, other medical problems influencing fatigue, or chronic fatigue syndrome). Scores above the 89th percentile were considered to be high.

Mood. The Hospital Anxiety and Depression Scale (HADS[22]) was used to investigate anxiety (HADS-A) and depression (HADS-D), higher scores indicating higher symptom frequency.

Outcome measures

Functional outcome was examined with the Glasgow Outcome Scale Extended (GOSE) [23,24] and scores were dichotomized into good outcome (7-8) and poor outcome (3-6). RTW was only assessed in patients who were employed or were actively seeking work before SAH. Questions about work resumption of the GOSE were used and answers were dichotomized into complete (able to work to previous capacity) and incomplete RTW (reduced work capacity or unable to work).

Statistical analyses

Statistical analyses were conducted using SPSS software (version 23.0, SPSS Inc.). Z-tests for difference of proportions were used to investigate if the proportions mental and physical fatigue were significantly different. Correlations were calculated to examine associations of fatigue with outcome (Spearman) and mood (Pearson), and between the two DMFS subscales (Pearson). Differences in fatigue levels between groups were investigated using independent t-tests, Mann-Whitney U tests, and two-way analysis of variance (ANOVA). Effect sizes (Cohen's *d*) were calculated. Binary logistic regression analysis (Enter method) was performed to determine the influence of Mental-f, Physical-f, HADS-A and HADS-D on the GOSE scores. Overall Alpha level was set at 0.05, with Bonferroni-Holm corrections in case of multiple comparisons.

Results

Participants

In total, 221 patients were included in this study (Fig. 1).

No significant differences were found between the patients who declined to participate and who responded, with respect to age, sex, or WFNS grade.

Table 1 shows the demographic and SAH characteristics of all patients.

Characteristics of fatigue and associations with mood

Compared to the norm group, 48.4% of all SAH patients reported high scores on Mental-f and 38.5% on Physical-f. The prevalence of mental fatigue was significantly higher than the prevalence of physical fatigue (Z-statistic for difference of proportions = 3, > critical value of 1.96, $p < 0.05$). The overlap between the presence or absence of mental and physical fatigue was 71.0%. The correlation between Mental-f and Physical-f was strong and positive (0.60). Significant and moderate correlations were found of Mental-f with HADS-A (0.54) and HADS-D (0.55) and of Physical-f with HADS-A (0.47) and HADS-D (0.58), all $ps < 0.05$.

Fatigue and SAH-related variables

Mental-f scores were significantly higher in patients with aSAH compared to patients with anSAH. Patients with CSF drainage had significantly higher scores on Physical-f and Mental-f than patients without drainage. Effect sizes for the significant differences were medium to high. No significant differences were found on the DMFS regarding other SAH-related variables (table 2). The results of a two-way ANOVA with both SAH type and external CSF drainage as independent variables and Mental-f as dependent variable, showed only a significant main effect of external CSF drainage, $F(1, 217) = 14.70, p < 0.001$. For Physical-f, no significant main and interaction effects (of either SAH type or CSF drainage) were found.

Fatigue and functional outcome

Poor outcome according to the GOSE (3-6) was found in 42.7% of all patients. RTW was determined in 131 patients, with incomplete RTW in 56.9%. Moderate negative correlations were found between DMFS and GOSE, indicating that higher levels of mental and physical fatigue were related to poor outcome (table 3). Effect sizes for significant differences of Mental-f and Physical-f between patients with poor and good outcome, as well as between complete and incomplete RTW, were large. Two-way ANOVAs revealed no significant interactions between external CSF drainage and both GOSE and RTW on Mental-f and Physical-f, all $ps > 0.05$.

A binary logistic regression analysis with the dichotomized GOSE score as dependent variable showed that outcome could be significantly predicted by a model including Mental-f, Physical-f, HADS-D and HADS-A ($\chi^2 = 52.99, p < 0.001, \text{Nagelkerke } R^2 = 0.32$). This model correctly classified 75.8% of patients. Table 4 shows that in this model, only Mental-f was a significant predictor of functional outcome; the odds of a patient with mental fatigue having unfavorable functional outcome were slightly higher than those of a patient without mental fatigue.

Discussion

This is the first study that investigated two major aspects of fatigue separately, namely mental and physical fatigue, and aimed to determine their mutual relationship with functional outcome in the chronic stage post-SAH. High frequencies of both mental and physical fatigue were found, with significantly more mental fatigue. Moreover, only mental fatigue was significantly related to unfavorable long-term functional outcome after SAH, compared to physical fatigue and mood problems.

In this study, mental fatigue was identified as an important factor post-SAH, in line with previous studies defining mental fatigue as most distinctive for brain injury [9,10]. Despite some overlap, our data support a distinction between mental and physical fatigue. Approximately one-third of all SAH patients was differently affected, either with mental or with physical fatigue. This corroborates the view that post-SAH fatigue is a multi-symptom construct, with mental and physical aspects. In previous studies, post-SAH fatigue was described as a unitary construct [3–5,25], addressed in questionnaires by just one single item or scored on scales designed for a non-neurological population [1,26]. This has caused a large variation in reported frequencies [1,2,6] and has led to an insufficient understanding of post-SAH fatigue. The current study also revealed that both mental and physical fatigue and mood are related phenomena after SAH. However, mental and physical fatigue were more prevalent than mood disorders; ergo, a significant proportion of SAH patients with mental or physical fatigue was not depressed or anxious. This all is in line with findings in other subtypes of stroke, in which the theoretical distinction between fatigue on the one side, and

depression or anxiety on the other side, is supported [27]. Furthermore, higher levels of mental fatigue only were found in aSAH patients in the present study. However, the differences in mental fatigue were, at least partly, explained by a higher rate of external CSF drainage after aSAH. In the literature, external drainage for hydrocephalus has been related to post-SAH cognitive dysfunction and unfavorable functional outcome [28]. Nevertheless, the association between mental and physical fatigue and functional outcome could not be explained by the need of external drainage for suspected increased intracranial pressure (in case of somnolence, or hydrocephalus on [acute] CT scan) in the present study. In addition, other SAH-related variables (i.e. treatment method, clinical condition on admission, shunting for persistent CSF resorption disturbances) were not significantly related to mental or physical fatigue.

Our study is the first to demonstrate that both mental and physical fatigue, though separately, are related to unfavorable long-term functional outcome after SAH. Around sixty percent of all included SAH patients did not return to work completely after SAH, consistent with previous studies [2,29]. SAH patients with poor functional outcome, including incomplete RTW, experienced significantly more mental and physical fatigue. The finding that only mental fatigue was significantly related to unfavorable functional outcome after SAH, in comparison to physical fatigue and mood disorders, shows the relevance of differentiating between both types of fatigue. A proper distinction may be very relevant for tailoring counseling of patients and their spouses. Previous studies only reported that greater fatigue was associated with poorer QoL [16,30] and impaired leisure resumption [17], but the influence of specific aspects of fatigue on RTW was unclear until now.

One of the limitations of our study is selection bias, due to patients who declined to participate. However, responders and non-responders did not differ significantly regarding demographic and SAH-related factors. Therefore we believe that our sample is fairly representative. Furthermore, the questionnaire used in our study (DMFS) has not been used before, therefore comparison with previous studies is difficult. However, the DMFS was specifically designed to measure fatigue in the chronic phase after brain injury and has been shown to have good psychometric

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properties [9]. There is growing evidence that the characteristics of fatigue after brain injury are different than in other patient groups, such as patients with chronic fatigue syndrome or cancer [7,8].

Thus, the use of a brain injury-specific scale as a way to measure different aspects of post-SAH fatigue can even be considered as a strength of the current study. Lastly, compared to previous studies [31], a relatively high percentage of patients were treated with external CSF drainage, possibly related to the indication used in our hospital; all cases with a decreased level of consciousness and suspected increased intracranial pressure, irrespective of a CT-scan showing enlarged ventricles or not, received either an EVD or ELD.

In conclusion, high frequencies of both mental and physical fatigue were found up to 10 years after SAH. Both types of fatigue were present, also in the absence of mood problems. Differences in fatigue levels between aSAH and anSAH patients could, at least partly, be explained by the need for early external CSF drainage. Moreover, mental fatigue was most prevalent after SAH and was the best predictor of functional outcome in the chronic stage, when compared to physical fatigue and mood disorders. Considering the multidimensional nature of post-SAH fatigue, mental and physical fatigue should be assessed separately. Moreover, distinguishing different aspects of post-SAH fatigue plausibly supports clinicians and researchers in improving treatment methods and may improve long-term functional outcome of SAH patients.

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Table 1. Characteristics of included SAH patients

	aSAH (N=166)	anSAH (N=55)
Number of women	114 (68.7%)	23 (41.8%)
Age at time of the SAH in years, mean (SD)	54.0 (10.0)	55.4 (10.2)
Time since SAH in years, mean (range)	6.8 (3-10)	6.9 (3-10)
WFNS		
Low (1-3)	131 (78.9%)	50 (90.9%)
High (4-5)	35 (21.1%)	5 (9.1%)
External CSF drainage (ventricular or lumbar)	84 (50.6%)	16 (29.1%)
VP-shunt for chronic hydrocephalus (after external drainage)	17 (10.2%)	1 (1.8%)
Treatment aSAH		
Clipping	57 (34.3%)	N/A
Coiling	107 (64.5%)	N/A
None	2 (1.2%)	N/A
Aneurysm circulation*		
Anterior	140 (84.3%)	N/A
Posterior	26 (15.7%)	N/A
Motor impairment		
Yes	4 (2.4%)	0 (0%)
No	162 (97.6%)	55 (100%)

Abbreviations: SAH, subarachnoid hemorrhage; aSAH, aneurysmal subarachnoid hemorrhage; anSAH, angiographically negative subarachnoid hemorrhage; WFNS, World Federation of Neurological Surgeons; CSF, Cerebrospinal Fluid; VP-shunt, ventriculo-peritoneal shunt; N/A, not applicable

*Anterior: aneurysms of the anterior cerebral or communicating artery, middle cerebral artery, posterior communicating artery, internal carotid artery, ophthalmic artery, and anterior choroidal artery. Posterior: aneurysms of the basilar artery, posterior cerebral artery, superior cerebellar artery, and vertebral artery.

Table 2. Scores on DMFS subscales and SAH-related variables

Characteristics	N	DMFS subscales							
		Mental-f				Physical-f			
		M (SD)	<i>t</i>	<i>p</i>	<i>d</i>	M (SD)	<i>t</i>	<i>p</i>	<i>d</i>
SAH-type									
aSAH	166	22.4 (7.1)	2.39	0.018*	0.36	17.0 (5.8)	1.50	0.14	0.24
anSAH	55	19.8 (7.5)				15.6 (6.0)			
WFNS									
Low (1-3)	181	21.3 (7.2)	-2.09	0.04	0.36	16.4 (5.7)	-1.47	0.14	0.26
High (4-5)	40	23.9 (7.3)				17.9 (6.3)			
External CSF drainage									
Yes	100	24.3 (6.6)	5.01	<0.001*	0.68	17.6 (5.9)	2.34	0.02*	0.32
No	121	19.6 (7.2)				15.8 (5.7)			
VP-shunt									
Yes	18	24.0 (6.4)	1.36	0.18	0.33	18.5 (5.9)	1.43	0.16	0.35
No	203	21.6 (7.4)				16.5 (5.8)			
Treatment aSAH									
Clipping	57	21.6 (7.0)	-1.06	0.29	0.17	17.2 (6.1)	0.46	0.65	0.07
Coiling	107	22.8 (7.2)				16.8 (5.7)			
Aneurysm circulation aSAH									
Anterior	140	22.3 (6.9)	-0.54	0.59	0.11	16.8 (5.8)	-0.78	0.44	0.17
Posterior	26	23.1 (8.1)				17.8 (5.7)			

Abbreviations: SAH, subarachnoid hemorrhage; aSAH, aneurysmal subarachnoid hemorrhage; anSAH, angiographically negative subarachnoid hemorrhage; WFNS, World Federation of Neurological Surgeons; CSF, Cerebrospinal Fluid; VP-shunt, ventriculo-peritoneal shunt; Mental-f, DMFS; Dutch Multifactor Fatigue Scale, Mental-f DMFS Mental fatigue; Physical-f, DMFS Physical fatigue

Note: Anterior: aneurysms of the anterior cerebral or communicating artery, middle cerebral artery, posterior communicating artery, internal carotid artery, ophthalmic artery, and anterior choroidal artery. Posterior: aneurysms of the basilar artery, posterior cerebral artery, superior cerebellar artery, and vertebral artery.

* significant differences after Bonferroni-Holm correction.

Table 3. Associations between DMFS subscales, GOSE and RTW

	Spearman correlations between DMFS subscales and GOSE			Mean scores on the DMFS subscales M (SD)				Good outcome vs. poor outcome			Complete vs. incomplete RTW		
	GOSE SAH	GOSE aSAH	GOSE anSAH	GOSE good outcome (7-8) N = 114	GOSE poor outcome (3-6) N = 85	Complete RTW N = 56	Incomplete RTW N = 74	<i>t</i>	<i>p</i>	<i>d</i>	<i>t</i>	<i>p</i>	<i>d</i>
Mental-f	-0.52*	-0.53*	-0.42*	18.6 (6.4)	25.4 (6.4)	17.8 (5.4)	24.8 (6.9)	-7.41	<0.001*	1.06	-6.36	<0.001*	1.13
Physical-f	-0.43*	-0.42*	-0.49*	14.4 (5.1)	19.0 (5.7)	13.6 (4.8)	18.3 (5.4)	-5.89	<0.001*	0.86	-5.13	<0.001*	0.94

DMFS, Dutch Multifactor Fatigue Scale; GOSE, Glasgow Outcome Scale Extended; RTW, return to work;

SAH, subarachnoid hemorrhage; aSAH, aneurysmal subarachnoid hemorrhage; anSAH, angiographically negative subarachnoid hemorrhage; Mental-f, DMFS Mental fatigue; Physical-f, DMFS Physical fatigue.

*significant differences ($p < 0.05$)

Table 4. Results of binary logistic regression on GOSE

	B (SE)	95% CI for Odds Ratio		
		Lower	Odds Ratio	Upper
<i>Included</i>				
Constant	-3.98 (0.72)*		0.02	
DMFS Mental-f	0.12 (0.03)*	1.05	1.12	1.19
DMFS Physical-f	0.05 (0.04)	0.98	1.05	1.14
HADS-D	0.08 (0.06)	0.97	1.08	1.21
HADS-A	-0.01 (0.05)	0.89	0.99	1.10

DMFS, Dutch Multifactor Fatigue Scale; Mental-f, DMFS Mental Fatigue; Physical-f, DMFS Physical fatigue, HADS-D, Hospital Anxiety and Depression Scale Depression; HADS-A, Hospital Anxiety and Depression Scale Anxiety.

* $p < 0.05$

Figure 1. Flow diagram of included and excluded patients

