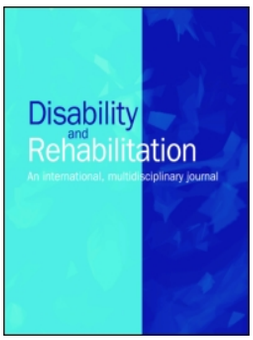

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RESEARCH PAPER

Long-term fatigue after perimesencephalic subarachnoid haemorrhage in relation to cognitive functioning, mood and comorbidity

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ABSTRACT

Purpose: To study relationships between fatigue and objective and subjective cognitive functioning, mood and comorbidity in the long term after perimesencephalic subarachnoid haemorrhage (PM-SAH).

Methods: Cross-sectional study. Objective cognitive functioning was measured with: Trail Making Test; Symbol Substitution; D2; Verbal and Semantic Fluency; Tower Test; Digit Span; 15-Words Test; Rey Complex Figure. Subjective cognitive functioning: Cognitive Failure Questionnaire. Fatigue: Fatigue Severity Scale. Mood: Hospital Anxiety and Depression Scale.

Results: Forty-six patients, mean age 50.4 (SD = 9.4), mean time after PM-SAH 4.7 (SD = 1.6) years participated. Patients with fatigue (33%) had significantly lower scores than patients without fatigue on most objective cognitive functioning tests ($p < 0.05$). Fatigue score was significantly associated with subjective and objective cognitive functioning, mood and comorbidity. After adjustment for mood and comorbidity, fatigue remained associated with attention and executive functioning.

Conclusions: This study supports our previous findings that a third of patients with PM-SAH experience fatigue and problems of cognitive functioning, also in the long term. Future research should investigate whether these patients would benefit from long-term follow-up and/or cognitive rehabilitation programmes.

➤ IMPLICATIONS FOR REHABILITATION

- Consequences for patients with PM-SAH are underestimated.
- One in every three patients suffered from fatigue in the long term after onset of PM-SAH.
- Patients with PM-SAH should be screened for problems of cognitive functioning, fatigue and mood in outpatient clinic just as patients with aneurysmal SAH.

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Cognitive functioning; fatigue; haemorrhage; mood; perimesencephalic; subarachnoid

Introduction

In about 10% of the cases of subarachnoid haemorrhage, patients are diagnosed with a perimesencepahlic subarachnoid haemorrhage (PM-SAH). This means that no aneurysm is found and the haemorrhage is restricted to the cisterns surrounding the brainstem and the suprasellar cistern, combined with a negative angiogram.[1,2] Although this type of subarachnoid haemorrhage (SAH) is often described as a benign form of SAH with favourable outcomes, we found that patients with PM-SAH may experience problems in executive functioning and fatigue in the short term.[3]

The long-term relationship between fatigue and cognitive functioning after PM-SAH has not extensively been studied. Most of the long-term outcome studies focus on clinical outcomes or quality of life.[4–7] In patients with aneurysmal SAH, long-term fatigue, which was present in 67% of patients, mood, and cognitive complaints were strongly associated with decreased health-related quality of life.[8] Despite good clinical outcome,[7] quality of life outcomes after PM-SAH are contradictory. Two studies [4,6] reported long-term complaints or reduced vitality and general health, whereas one study reported no long-term reduction in quality of life.[5] Hutter et al.,[9] Madureira et al. [10] and Krajewski et al. [11] did focus on cognitive outcomes in patients with PM-SAH or other types of non-aneurysmal SAH (broader group). They determined minor cognitive deficits in their patients, but did not study fatigue in relation to cognitive functioning. In an earlier study, we found that 38% of the subgroup of patients with PM-SAH ($n = 8$) suffered from fatigue 3.2 (SD 2.5) months post onset.[3] In view of the expected favourable outcome in patients with PM-SAH, we considered this a surprising outcome that asked for replication in a larger population. The data registries of two university medical centres were used to obtain a larger group of patients with PM-SAH that could be tested extensively on cognitive functioning. We were interested whether the experienced cognitive problems that were found around three months after PM-SAH also exist in the long term. The aim of this study was to investigate the relationships between

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fatigue, cognitive functioning and mood on the long term after PM-SAH. The second aim was to determine whether cognitive functioning differs between patients with and without fatigue after PM-SAH. If fatigue is related to problems in cognitive functioning, than this should be taken into account in tailoring (cognitive) rehabilitation programmes for these patients.[12]

Methods

Participants and procedures

All patients diagnosed with PM-SAH, hospitalized between 2006 and 2012 at the neurology and neurosurgery departments from the Erasmus University Medical Centre Rotterdam or the University Medical Center Utrecht, were screened for participation in this study. PM-SAH was defined by accumulation of blood around the mesencephalon on CT and a normal four-vessel angiogram. Inclusion criteria were: PM-SAH, and at least 18 years of age. Exclusion criteria were: all other types of stroke or SAH, serious (neurological) comorbidity and insufficient mastering of the Dutch language. All patients who were willing to participate provided informed consent. The Medical Ethics Committee of the Erasmus MC and UMC Utrecht approved the study.

Data collection

The staff of the neurology and neurosurgery departments in both hospitals identified all patients diagnosed with PM-SAH from a data registry of all SAH patients hospitalized between 2006 and 2012. Patients received an information letter from their neurologist and were invited to participate in the study. After informed consent was obtained from eligible patients, a research psychologist visited the patients at home to collect various outcome measures. A structured interview was used (patient characteristics and pre- and post-injury employment status), and validated questionnaires for depression, fatigue, comorbidity and subjective cognitive functioning. Furthermore, objective tests were used for multiple domains of cognitive functioning, which included memory, executive functioning, attention, concentration, speed of information processing and visuoconstruction. We designed our study in such a way that we assessed fatigue in the first part of the test battery in each patient. Furthermore, all tests were provided in a fixed order, alternating between questionnaires and cognitive tests with regular breaks in between.

Measurement instruments

Questionnaires

Fatigue was assessed using the Fatigue Severity Scale (FSS). The questionnaire contains nine statements on fatigue in daily life. The patients score these statements on a 7-point Likert scale ranging from 1 to 7, with 1 indicating "Strongly Disagree" and 7 indicating "Strongly Agree". The fatigue score is the mean score of these nine items. Subgroups of patients with and without fatigue were studied using a cut-off value of 4 or higher.[13–15]

The Cognitive Failure Questionnaire (CFQ) measures self-perceived cognitive failures in daily life. It consists of 25 items for which participants indicate on a 5-point scale (range 0–4) how often they experience cognitive failures in daily life. A sum score is calculated (range 0–100) in which higher scores indicate an increased experience of cognitive problems.[16] "Normal" scores range from 21 to 43 (mean 31.8, SD 11.1), a cut-off score >43 is used to distinguish normal scores from abnormal scores.[17]

To measure the degree of depression and anxiety in patients, the Hospital Anxiety and Depression Scale (HADS) was used. This questionnaire exists of seven questions related to anxiety and seven related to depression. The answers are given on a 4-point scale (range 0–3) and a total sum score is calculated. A higher sum score indicates more emotional problems. The scores 0–7 are defined as no anxiety or depression, 8–10 as probable cases and 11–21 as definite cases.[18,19]

Comorbidity was measured with the Cumulative Illness Rating Scale (CIRS). This list consists of 14 disorders and diseases (including SAH), which are rated on a 5-point rating scale, ranging from 0 (disorder/disease not present) to 4 (life-threatening disorder/disease present).[20] Patients were classified as having symptoms of comorbidity if they had a sum score above 5.[21]

Neuropsychological tests

The Trail Making Test (TMT) was used to measure cognitive functioning on the domains speed of information processing (part A) and divided attention, which was classified as a task of executive functioning (part B). The measured time to complete the task (with a maximum of 180 s), including extra time for correcting potential errors, was recorded to calculate a time score.[22,23] Norm scores by age group and education were obtained from Tombaugh.[24]

The D2 test of attention and concentration was used to measure visual selective attention, processing speed and concentration. A total performance score and a concentration performance score was determined. The total performance score was calculated from the total of processed items minus total missed items and total wrong items; the concentration performance score is based on the total identified correct items minus total identified wrong items.[25]

The Digit Span is a subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III), and was used to measure attentional span and working memory. The maximum scores for the forwards and backwards series are 16 and 14, respectively.[26]

The Symbol Substitution task (SS) is a subtest of the WAIS-III, and was used to measure speed of information processing. The total number of correctly completed items is counted.[26]

The Fifteen Word Task (15WT, Dutch version) was used to measure learning, delayed recall and recognition. Raw scores were calculated for the immediate total (15WT-TRS) recall (range 0–75), delayed (15WT-DRS) recall (range 0–15) and for the recognition task (15WT-rec) (range 0–30). A cut-off score ≤ 26 is used to distinguish normal scores from abnormal scores for the recognition task.[27]

To measure semantic memory (category fluency) and executive functioning (phonological fluency), the Word Fluency (WF) task was used. The total score consists of the total correct items in, respectively, 2 and 1 min named per task.[28]

The Tower Test (TT) from the Delis–Kaplan Executive Functioning System measures executive functions like planning and problem-solving abilities. A total performance score is calculated taking time and total amount of moves into account.[29]

The Rey Complex Figure Task (RCFT) was used to measure visuoconstructional skills (copy) and incidental memory (recall). Patients receive points for correctly placed lines, the total score for both copies is used.[27]

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 21 (SPSS Inc., Chicago, IL). Descriptive statistics were used to describe the study population characteristics. Means and standard deviations were calculated for interval variables and numbers and percentages for categorical variables. Differences in patients, SAH

characteristics and cognitive outcomes between fatigued and non-fatigued patients, were tested with independent samples *T*-Tests. Dichotomous or categorical variables were calculated with a chi-square or Fisher's Exact test in the case of small groups. Relationships between subjective and objective cognitive test outcomes, fatigue, depression scores and comorbidity scores are expressed in Pearson correlations. Relationships between fatigue and cognitive functioning were adjusted for depression and comorbidity using partial correlations. *T*-scores were calculated based on clinical reference scores, adjusted for age and education level for each individual. *T*-scores in the range of 40–60 are considered normal.[25–29] The mean scores of TMT and CFQ were also compared with published norms using independent samples *T*-tests.[17,24] A significance level of $p < 0.05$ was used for all analyses. Bonferroni corrections were performed to correct for multiple testing for the comparisons between patients with and without fatigue, resulting in a significance level of $p < 0.003$.

Table 1. Demographic and clinical characteristics of patients with PM-SAH.

	Total group $N = 46$
Age of onset, years, mean ± SD	50.4 ± 9.4
Gender, men, *n* (%)	29 (63.0)
Partner, yes, *n* (%)	39 (84.8)
Education, high, *n* (%)	19 (41.3)
Hypertension, yes, *n* (%)	12 (26.1)
CIRS total score, mean ± SD	4.0 ± 3.0
Pre-morbid employment status, *n* (%)	
Employed	36 (78.3)
Retired	4 (8.7)
Unemployed	6 (13.0)
Current employment status, *n* (%)	
Employed	29 (63.0)
Retired	7 (15.2)
Unemployed	10 (21.7)
Hospital discharge destination, *n* (%)	
Home	45 (97.8)
Inpatient rehabilitation	1 (2.2)
Time post onset (years), mean ± SD	4.7 ± 1.6
FSS (fatigue score), mean ± SD	3.4 ± 1.3

CIRS: Cumulative Illness Rating Scale; FSS: Fatigue Severity Scale.

Results

Study population

From a total of 109 patients with PM-SAH, 19 patients were excluded based on the exclusion criteria, 20 did not respond, and 24 were not interested. In total, 46 patients agreed to participate in the study; 20 from Erasmus MC Rotterdam and 26 from University Medical Center Utrecht. The mean age of the total group was 50.4 (SD 9.4) years, and 63% were men. An overview of the patient- and clinical characteristics is displayed in Table 1. In this study sample 33% suffered from fatigue ($n = 15$; mean 3.4; SD 1.3). Patients with fatigue were less likely to have a paid job after PM-SAH, although not significantly (40% vs 74%, $p = 0.075$). Furthermore, patients with fatigue had more hypertension (47% vs 16%, $p = 0.038$), and higher scores on the CIRS comorbidity scale than patients without fatigue (mean 6.5, SD 3.5 vs mean 2.8, SD 1.7; $p = 0.001$). The other characteristics did not differ significantly between patients with and without fatigue.

Comparison between fatigued and non-fatigued patients and norms

Patients with fatigue did not differ significantly from patients without fatigue in subjective cognitive functioning, but they did have significantly poorer scores on depression and on the objective cognitive functioning domains of attention and concentration, speed of information processing, and memory (Table 2).

Table 2. Mean scores and differences in Cognitive Test outcomes and Depression; Fatigued (FSS ≥4) vs Non-Fatigued (FSS <4) patients with PM-SAH.

	Fatigued $n = 15$ mean ± SD	Non-Fatigued $n = 31$ mean ± SD	Fatigued vs Non-Fatigued *p* values
HADS (depression score), mean ± SD	6.4 ± 3.0	2.1 ± 3.0	**<0.001**
Probable depression HADS ≥8, n (%)	5 (33.3)	2 (6.5)	**0.029**
Subjective cognitive functioning			
CFQ, Total score	42.2 ± 15.4[a]	33.5 ± 13.5	0.056
CFQ Score >43, *n* (%)	7 (46.7)	4 (12.9)	**0.024**
Attention and concentration			
D2, Concentration performance	137.2 ± 39.9	179.6 ± 31.1	**0.001**[b]
Digit Span, Forward	7.6 ± 1.2	9.0 ± 1.8	**0.007**
Speed of information processing			
D2, Total performance	353.2 ± 99.8	450.3 ± 79.2	**0.001**[b]
TMT A (max 180 s)	39.1 ± 11.6[a]	28.6 ± 8.8	**0.001**[b]
Symbol Substitution (total good)	56.5 ± 17.6	75.8 ± 13.3	**<0.001**[b]
Memory			
15 WT, Total score	38.5 ± 10.1	46.6 ± 8.6	**0.007**
15 WT, Total recall	7.3 ± 3.0	10.1 ± 2.4	**0.001**[b]
15 WT, Total recognition	28.3 ± 1.2	29.3 ± 1.2	**0.006**
Rey Complex Figure, Recall score	17.5 ± 6.5	21.0 ± 5.0	0.051
WF, Semantic	31.4 ± 7.9	36.4 ± 7.3	**0.042**
Digit Span, Backward	5.6 ± 1.5	6.9 ± 2.4	0.061
Digit Span, Total score	13.3 ± 2.5	15.9 ± 3.6	**0.014**
Executive functioning			
TT, Total performance	15.4 ± 4.4	18.2 ± 4.5	0.067
WF, Phonological	19.5 ± 5.0	25.1 ± 7.6	**0.014**
TMT B (max 180 s)	87.8 ± 40.3[a]	69.0 ± 23.5	0.052
Visuoconstruction			
Rey Complex Figure, Copy score	33.1 ± 2.7	33.1 ± 2.5	0.939

HADS: Hospital Anxiety and Depression Scale; CFQ: Cognitive Failure Questionnaire; TMT: Trail Making Test; 15 WT: 15 Words Task; WF: Word Fluency.
[a]Mean scores worse than healthy individuals ($p < 0.05$).
[b]Significant after Bonferroni correction ($p < 0.003$).
Bold values are significant ($p < 0.05$)

Comparing the *T*-scores, which were adjusted for age and education level, we found that the proportion of patients with abnormal test results was significantly larger in the fatigued group than in the non-fatigued group for the D2 Concentration performance, D2 Total performance, TMT A and SS (Table 3).

Furthermore, in the fatigued group, total mean scores on TMT A ($t = 2.3$; $p = 0.023$) in the speed of information processing domain, TMT B ($t = 3.3$; $p = 0.002$) in the executive functioning domain, and CFQ ($t = 3.6$; $p < 0.001$) in subjective cognitive functioning were significantly worse than those from healthy individuals.[24]

Table 3. Proportions of patients with abnormal test results (*T*-scores <40, adjusted for age and education level) for Fatigued (FSS ≥4) vs Non-Fatigued (FSS <4) patients with PM-SAH.

	Fatigued $n = 15$ % abnormal	Non-Fatigued $n = 31$ % abnormal	Fatigued vs Non-Fatigued *p* values
D2, concentration performance	28.6	0.0	**0.007**
D2, total performance	50.0	6.5	**0.002**[a]
Digit Span, Total score	20.0	6.5	0.311
15 WT, Total score	33.3	9.7	0.092
15 WT, Total recall	33.3	12.9	0.127
15 WT, Total recognition	6.7	6.5	0.704
Rey Complex Figure, Copy score	20.0	9.7	0.375
Rey Complex Figure, Recall score	46.7	22.6	0.170
Symbol substitution (total good)	20.0	0.0	**0.030**
TMT A (max 180 s)	33.3	0.0	**0.002**[a]
TMT B (max 180 s)	20.0	6.5	0.311
TT, total performance	13.3	0.0	0.101
WF, semantic (1 min)	26.7	12.9	0.414
WF, phonological	26.7	23.3	1.000

TMT: Trail Making Test; 15 WT: 15 Words Task; WF: Word Fluency.
Missings: D2: $n = 1$; Tower Test: $n = 1$.
[a]Significant after Bonferroni correction ($p < 0.003$).
Bold values are significant ($p < 0.05$)

Relationships between fatigue, depression, comorbidity and cognitive functioning

In Table 4, the correlations between fatigue, subjective and objective cognitive functioning, depression and comorbidity scores are presented. Strong correlations were found among fatigue, depression and comorbidity. Higher fatigue scores were related to poorer cognitive functioning on all domains (subjective and objective), except for visuoconstruction. Depression score was associated with poorer scores of subjective cognitive functioning, attention and concentration, and memory. Comorbidity score was negatively associated with the domains of processing speed, attention and concentration, and memory. Subjective cognitive functioning (CFQ) was not associated with any domain of objective cognitive functioning. Partial correlations showed that the relationships between fatigue and Digit Span (forwards) ($p = 0.032$), Symbol Substitution (total good) ($p = 0.041$), 15WT (total good score) ($p = 0.041$), WF (semantic) ($p = 0.021$) and WF (phonological) ($p = 0.011$) remained significant, adjusted for depression. These variables still covered all the domains of objective cognitive functioning, except the domain visuoconstruction. Adjusting for both depression and comorbidity, revealed that relationships between fatigue and Digit Span (forwards) ($p = 0.019$) and WF (phonological) ($p = 0.010$) remained significant.

Discussion

The main finding in this study was that 1 in every 3 patients suffered from fatigue in the long term after onset of PM-SAH. Fatigue was strongly related to poorer scores on both subjective and objective cognitive functioning, depression, and comorbidity. Higher depression and comorbidity scores were also related to reduce objective cognitive functioning. However, only fatigue was associated with the domain of executive functioning, also after

Table 4. Pearson correlations between Fatigue, Subjective and Objective cognitive test outcomes, Depression score, and Comorbidity score.

	FSS Total score *r* (*p* values)	HADS Depression *r* (*p* values)	CIRS Total score *r* (*p* values)	CFQ Total score *r* (*p* values)
FSS Total score	1	0.597 (<0.001)	0.473 (0.001)	0.405 (0.005)
HADS Depression	0.597 (<0.001)	1	0.419 (0.004)	0.372 (0.011)
CIRS Total score	0.473 (0.001)	0.419 (0.004)	1	–
Subjective cognitive functioning				
CFQ Total score	0.405 (0.005)	0.372 (0.011)	–	1
Attention and concentration				
D2 Concentration performance	−0.351 (0.018)	–	−0.371 (0.012)	–
Digit span, forwards	−0.545 (<0.001)[a,b]	−0.353 (0.016)	–	–
Speed of information processing				
D2 total performance	−0.326 (0.029)	–	−0.387 (0.009)	–
TMT A (max 180 s)	0.369 (0.012)	–	–	–
Symbol substitution (total good)	−0.454 (0.002)[a]	–	−0.413 (0.004)	–
Memory				
15 WT Total score	−0.408 (0.005)	−0.383 (0.009)	−0.334 (0.023)	–
15 WT Total recognition	−0.314 (0.034)	−0.427 (0.003)	−0.467 (0.001)	–
15 WT Total recall	−0.410 (0.005)	−0.327 (0.026)	−0.324 (0.028)	–
Rey Complex Figure, Recall score	−0.399 (0.006)	–	–	–
WF, semantic	−0.371 (0.011)	–	−0.406 (0.005)	–
Digit span, backwards	−0.335 (0.023)[a]	–	–	–
Digit span, total score	−0.476 (0.001)	−0.352 (0.017)	–	–
Executive functioning				
TT, Total performance	−0.368 (0.017)	–	–	–
WF, phonological	−0.453 (0.002)[a,b]	–	–	–
TMT B (max 180 s)	–	–	–	–
Visuoconstruction				
Rey Complex Figure, Copy score	–	–	–	–

CFQ: Cognitive Failure Questionnaire; TMT: Trail Making Test; 15 WT: 15 Words Task; WF: Word Fluency; FSS: Fatigue Severity Scale; CIRS: Cumulative Illness Rating Scale; HADS: Hospital Anxiety and Depression Scale.
[a]Significant partial correlations adjusted for depression $p < 0.05$.
[b]Significant partial correlations adjusted for depression and comorbidity $p < 0.05$.

adjustment for depression and comorbidity. This is in line with the results from our previous study.[3]

Fatigue after A-SAH is often described in the literature. The review of Kutlubaev et al. [15] mentioned pituitary dysfunction as a potential predictor for post A-SAH fatigue. In patients with stroke and TIA, associations between fatigue and both hyper- and hypotension have been found.[30] Wu et al. [31] make a distinction in early fatigue, which may be triggered by biological factors, such as inflammatory and neuroendocrine changes after stroke, and late fatigue, which may be more attributable to psychological and behavioural factors. Relationships between fatigue and factors such as anxiety, depression, PTSD, memory difficulties, personality changes, sleep disturbances and cognitive and physical impairment after A-SAH have been described.[15,32] In this study, relationships of fatigue with cognitive functioning and depression are also found in PM-SAH patients. Pihlaja et al. [33] presented similar associations of fatigue with negative cognitive outcomes, and lower rates of return to work 3–6 months after stroke. The employment rate of patients with fatigue in our study was relatively low (40.0%) compared with patients without fatigue (74.2%), although not significantly different. The total employment rate in our patients with PM-SAH (63%) was comparable to the return-to-work rate after A-SAH (61.4%), despite the presumed favourable outcome.[34]

Comparing the proportions of abnormal test scores between the fatigued and non-fatigued group we found significant differences in subjective cognitive functioning, attention and concentration, and speed of information processing. Furthermore, patients with fatigue experienced more subjective cognitive complaints and underperformed healthy individuals on the TMT A and B tasks for speed of information processing, and executive functioning.[17,24] These results support the findings from our previous work in a relatively small group of patients with PM-SAH ($n = 8$), in which fatigue and executive functioning were affected.[3] Krajewski et al. [11] also found tendencies of memory impairment and slower cognitive processing in PM-SAH groups two years after discharge, but they found no significant differences compared with norm data. However, they did not perform subgroup analyses in patients with fatigue.

Because of the good prognosis, in terms of no risk of re-bleeds and unaffected survival rates, patients with PM-SAH are mostly discharged home without follow-up. Moreover, this group of patients is often excluded from scientific research, because of the assumed good prospects. The outcomes of our study question this assumption. Patients with PM-SAH could be followed in outpatient rehabilitation clinics to screen for problems of cognitive functioning, fatigue and mood. There are simple screening questionnaires like the FSS and HADS available as a starting point for screening. Subjective cognitive functioning appeared not to be related to objective cognitive functioning.[17] Our results suggest that screening for subjective cognitive problems (CFQ) may not be sufficient in detecting specific problems of cognitive functioning.

This study has some limitations. Despite the fact that with a larger number of patients we confirmed the results of our previous study, the sample size is still small. Also, the absence of short-term measurements and follow-up measurements can be considered a limitation of this study, because no causal relationships could be studied. Another limitation may be that the test battery was quite long and intensive for the patients, which may have resulted in fatigue at the end of the session. This could have influenced performance on lengthy cognitive tests. We anticipated this problem by assessing fatigue in the first part of the test battery. At last, not all patients that were contacted responded or were interested in taking part in this study, which may have resulted in selection bias.

In conclusion, this study supports our findings from previous research that the consequences for patients with PM-SAH are underestimated. These patients may be left with fatigue, have less than optimal cognitive functioning, and relatively low employment rates. Patients with PM-SAH should be screened for these problems in outpatient clinic just as patients with aneurysmal SAH. Future research should investigate whether these patients would benefit from long-term follow-up and/or rehabilitation programmes incorporating fatigue management and/or cognitive rehabilitation.

Disclosure statement

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit on the authors or on any organization with which the authors are associated.

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