COGNITIVE & PSYCHOSOCIAL OUTCOMES AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE

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COGNITIVE & PSYCHOSOCIAL OUTCOMES AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE

Cognitieve en psychosociale uitkomsten na een aneurysmale subarachnoïdale bloeding
(met een samenvatting in het Nederlands)

Proefschrift

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door

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geboren op 5 december 1984
te Leiden

Promotoren:	Prof. dr. G.J.E. Rinkel
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Co-promotor:	Dr. M.J.E van Zandvoort

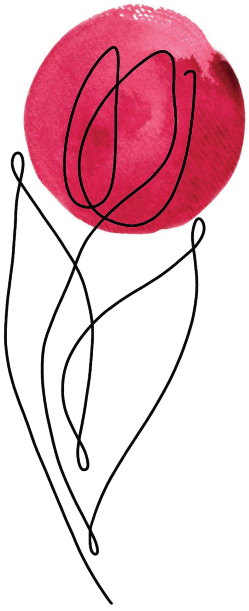
"Don't it always seem to go that you don't know what you got till it's gone"

Joni Mitchell

CONTENT

CHAPTER 1

General Introduction



GENERAL INTRODUCTION

"What I remember is that I was gardening, when suddenly I experienced the worst headache I've ever had. The next thing I remember is that I was in hospital. First there was an overwhelming feeling of relief that I had survived the bleeding, recovered well and was able to go home. But, since then, I've been trying to get my life back on track; I admit that I'm struggling. Although I don't have any physical defects, the hemorrhage has had a huge impact on my life."

ANEURYSMAL SUBARACHNOID HEMORRHAGE (ASAH)

The 47-year-old woman in this story was diagnosed with an aneurysmal subarachnoid hemorrhage (aSAH). An aSAH is a bleeding in the subarachnoid space that is caused by a rupture of an intracranial aneurysm. aSAH accounts for 5% of all strokes.[1] Around 3% of the general population worldwide have an unruptured intracranial aneurysm,[2] which is a local weakness of an intracranial artery wall that has developed into a bulge. Aneurysms generally develop above the age of 30 and are more present in women, in individuals with a family history of aSAH and in those with autosomal dominant polycystic kidney disease (ADPKD).[3] Key environmental risk factors affecting aneurysms are smoking and hypertension. The chances of an intracranial aneurysm rupturing are small. The incidence of aSAH worldwide is around 6 per 100,000 per year.[4] With a mean age of onset around 55 years, aSAH patients are relatively young.[5]

One of the main clinical characteristics of an aSAH is an acute onset of an extremely severe headache.[6] Around half of patients lose consciousness at onset.[7] Other symptoms are nausea, vomiting, focal neurological deficits (often temporary) and in some cases seizures.[6] After several hours, neck stiffness can develop. The case-fatality rate is high; around 35% of patients die directly after onset or within one month after aSAH.[8] Of those patients who reach hospital alive, the ruptured aneurysm can be occluded either by endovascular treatment (e.g. coiling) or by a surgical procedure (clipping). Because of the risk of neurological complications after aSAH, patients often stay hospitalized for a minimum of one or two weeks.[9] A small proportion (10-20%) of aSAH survivors are dependent on help in terms of activities of daily living (ADL) after aSAH[10] and are therefore admitted to a nursing home or rehabilitation center. Most of the patients who survive the initial weeks, however, are ADL-independent and go home after discharge.[9]

Although most of these patients have good functional outcomes (mobility and ADL), they often cannot regain their pre-morbid level of activities and (social) participation.[11] Patients experience difficulties with complex activities such as managing finances, shopping or

housekeeping, but also in taking up their previous role in the family or in society. Of the patients who had a job at the time of the aSAH, almost two-thirds return to their pre-SAH employment, but only one-third resume this job completely.[12] Moreover, around half of patients report changes in social participation and cannot resume pre-SAH leisure activities, even in the long term.[13,14] According to the International Classification of Functioning, Disability and Health (ICF) the level of activities and participation in patients with a health condition are related to body functions & structures such as psychical, cognitive, emotional (dis)functions, pathophysiology and anatomical structures or impairments.[15] Body functions & structures, activities and participation together determine patients' quality of life. To help patients recover, insight into all of these factors is important and a holistic approach is required in which these factors are integrated. This thesis therefore focuses on the pathophysiological, cognitive and emotional consequences and level of social participation after aSAH, as well as how these factors are interrelated.

COGNITIVE OUTCOMES AFTER ASAH

Cognitive complaints are reported in up to 80% of ADL-independent aSAH patients.[16] Mental slowness and short-term memory problems are the most frequently reported cognitive complaints, followed by attention problems. Some of these cognitive complaints can be explained by underlying cognitive deficits, as measured by a neuropsychological examination. With a prevalence up to 83%, cognitive deficits are common after aSAH.[11] These deficits are most prominent during the first months after aSAH, but often persist for years.[17,18] Deficits in memory and executive functioning are most commonly detected,[11] but deficits in other cognitive domains such as attention, language, visuospatial functioning, and reaction time are also frequently found.[19-21] That several and often multiple cognitive domains can be affected after aSAH might reflect a diffuse nature of injury after the hemorrhage.[11,19] Brain injury after aSAH is caused by different processes. In the acute phase after an aSAH the intracranial pressure (ICP) rises and the cerebral blood flow (CBF) decreases, both leading to a decrease in cerebral perfusion which might result in cerebral ischemia.[22,23] In some patients rebleeding of the aneurysm occurs, which leads to further brain damage. Moreover, in the subacute phase, aSAH patients are at risk of secondary complications such as delayed cerebral ischemia (DCI) and hydrocephalus.[24] Although previous research has concentrated on the pathophysiological events after an SAH and its relationship to cognitive outcome, the exact cause of cognitive deficits and cognitive complaints after an SAH is still unclear.

PSYCHOSOCIAL OUTCOMES AFTER ASAH

Health-related quality of life after aSAH is determined not only by cognitive complaints, but also by other factors, such as fatigue and mood disorders.[25] With a prevalence up to 90%, fatigue is the most frequently self-reported complaint after aSAH.[16] Moreover, half of aSAH patients experience feelings of depression and/or anxiety.[11] These mood disturbances are sometimes attributed to the presence of cognitive deficits, but more often patients' beliefs in the chronic nature of their medical condition and fear of a recurrent hemorrhage play a role.[26,27] In contrast to this future-oriented fear, some aSAH patients have intrusive thoughts about the past experience of the aSAH itself or avoid reminders of this traumatic event. The prevalence of Posttraumatic Stress Disorder (PTSD) after aSAH varies between 18% and 37%.[27,28] In most of the patients, symptoms of depression and anxiety after aSAH remain stable during the first 18 months after aSAH.[17,18] To what extent PTSD symptoms change over time is unclear.[11]

AIM OF THE THESIS

The aim of this thesis is to better understand why there is a very heterogenous pattern of clinical outcomes in aSAH patients, even when they are ADL-independent. In part I we investigate determinants of cognitive outcomes 3 months after an aSAH. Part II concentrates on determinants of the course of PTSD and participation (psychosocial outcomes) during the first year after an aSAH.

STUDY POPULATION

Data on patients included in the studies for this thesis were retrieved from a prospectively collected series of aSAH patients who were admitted to the University Medical Center Utrecht (UMCU) and visited the SAH outpatient clinic. According to clinical routine in the UMCU, all patient discharged from the hospital to home or to a rehabilitation institution on a temporary basis are invited to the SAH outpatient clinic 3 months after the SAH. Here, patients are interviewed by a nurse practitioner specialized in SAH, undergo a neuropsychological examination by a neuropsychologist, and visit a rehabilitation physician for a physical examination and to assess the need for additional therapy.

OUTLINE

PART I: Determinants of cognitive outcomes after an aSAH

In the study in **Chapter 2** we focus on the initial impact of the hemorrhage on cerebral perfusion and its relationship with cognitive functioning after an aSAH. In **Chapter 3** the relationship between cerebral ischemia and both cognitive complaints (subjective) and cognitive functioning (objective) after an aSAH is studied. Magnesium sulfate is a neuroprotective agent that might help to prevent cerebral ischemia after aSAH.[29] In a randomized clinical trial (**Chapter 4**) we assessed if treatment with magnesium also has an effect on cognitive functioning after aSAH. The role of ventricular volume in cognitive outcomes (both complaints and functioning) after aSAH is investigated in **Chapter 5**.

PART II: Determinants of psychosocial outcomes after an aSAH

In **Chapter 6** we examined individual differences in the course of PTSD symptoms during the first year after an aSAH and explored which factors are related to this. In **Chapter 7** we studied to what extent patients experience restrictions and dissatisfaction with the level of (social) participation 6 months after an aSAH and examined possible predictors of participation after an aSAH. In order to investigate the course of participation, we also assessed the level of participation 3 and 12 months after an aSAH. **Chapter 8** focuses on determinants of the course of participation after an aSAH. In **Chapter 9** the main findings of this thesis are discussed, as well as implications for clinical care and suggestions for future research.

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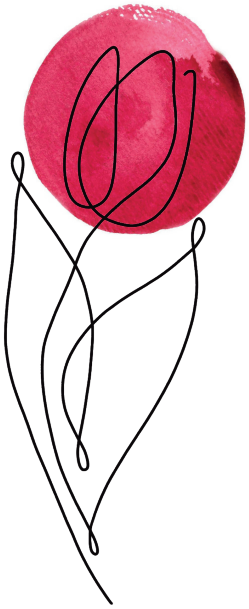
PART I

Determinants of cognitive outcome after aSAH

CHAPTER 2

CT Perfusion on admission and cognitive functioning 3 months after aneurysmal subarachnoid hemorrhage



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ABSTRACT

Introduction

Many survivors of aneurysmal subarachnoid hemorrhage (aSAH) have persistent cognitive deficits. Underlying causes of these deficits have not been elucidated. We aimed to investigate if cerebral perfusion in the acute phase after aSAH measured with CT perfusion (CTP) is associated with cognitive outcome 3 months after aSAH.

Methods

We included 71 patients admitted to the University Medical Center Utrecht who had CTP performed within 24 hours after ictus and neuropsychological examination after 3 months. Perfusion values were measured in predefined regions of interest for cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to peak (TTP). The relationship with global cognitive functioning, as measured with a mean *z*-score of all cognitive tests, was examined by linear regression analyses. Adjustments were made for age, education, method of aneurysm treatment, and presence of non-acute medical complications.

Results

TTP was associated with cognitive functioning in the univariable analysis (B = -0.042, 95% CI -0.076 to -0.008), but not after adjustment for age (B = -0.030, 95% CI -0.065 to 0.004). For CBF, CBV and MTT no relationship with cognitive functioning was observed.

Conclusions

Cerebral perfusion measured with CTP within 24 hours after onset of aSAH is not associated with cognitive outcome after 3 months. The lack of an association might be explained by the delay between onset of aSAH and CTP. However, CTP assessment within the first minutes after aSAH is impossible in large series of patients.

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is associated with substantial case fatality and morbidity. Although survivors of aSAH often regain independence in basic activities of daily living (ADL), many have persistent cognitive deficits across multiple cognitive domains.[1] These cognitive deficits often lead to restrictions in daily activities and are related to a decreased long-term health-related quality of life.[2]

Several studies aimed to elucidate which factors after aSAH explain these cognitive deficits.[1] It has been suggested that measures of the extent of the hemorrhage or the impact of the hemorrhage such as the amount of extravasated blood,[3,4] the initial condition of the patient,[5] global cerebral edema,[6] and acute hydrocephalus[5] are related to cognitive deficits. However, these factors only explain a part of the variance of the cognitive deficits after aSAH. A better marker of the initial impact of the hemorrhage may be cerebral perfusion. We, therefore, studied the relationship between CT perfusion on admission and cognitive outcome 3 months after aSAH.

METHODS

Design

This study was approved by the Medical Ethics Review Committee of the University Medical Center of Utrecht. Patients were retrieved from a prospectively collected series of aSAH patients admitted to the University Medical Center Utrecht between September 2006 and August 2008. In our institution all patients with aSAH routinely undergo non-contrast CT (NCCT), CTP and CT-angiography (CTA) on admission, unless there are contraindications for CT with contrast, such as pregnancy or impaired renal function. Patients discharged from the hospital to home or to a rehabilitation institution on a temporary basis, are invited to the SAH outpatient clinic 3 months after SAH. Here, patients are interviewed by a nurse practitioner specialized in SAH, visit a rehabilitation physician for a physical examination, and undergo a neuropsychological examination by a neuropsychologist. Inclusion criteria for this study were: (1) 18 years of age or older; (2) CTP scan made <24 hours after ictus; and (3) neuropsychological examination at the SAH outpatient clinic. Exclusion criteria were: (1) aSAH in medical history; (2) movement artefacts on CTP imaging or other CTP failures.

CTP imaging

The imaging studies were performed on a 16 or 64-multidetector CT scanner (Philips Mx8000 IDT 16, Philips Brilliance 16P, Philips Brilliance 64; Best, the Netherlands). For the CTP scan 40 mL of non-ionic contrast agent (Iopromide, Ultravist, 300 mg iodine/mL, Schering, Berlin, Germany) was injected into the cubital vein (18 gauge needle) at a rate of 5 mL/s followed by 40 mL saline flush at a rate of 5 mL/s using a dual power injector (Stellant Dual CT injector, Medrad Europe BV, Beek, the Netherlands). The following parameters were used: 16 slice, 90 kVp, 150 mAs, 8x3 mm collimation; 64 slice, 80 kVp, 150 mAs, 64x0.625 mm collimation. For both scanners, 1 image was acquired per 2 seconds from initiation of contrast injection during 60 seconds, with a 512x512 matrix, a field of view ranging from 160 to 220 mm, UB filter and standard resolution.

CTP post-processing

CTP scans were reconstructed to 5 mm slices for the 64- and 6 mm slices for the 16-multidetector CT scanner. Perfusion data were analyzed using free software package called Perfusion Mismatch Analyzer (PMA, version 4.0.4.4, ASIST Japan). The arterial input function (AIF) was automatically selected by PMA, and manually corrected if the automatic selection failed. A time-insensitive CTP algorithm, block-circulant singular value decomposition (bSVD),[7] was used to calculate cerebral perfusion maps for four different perfusion parameters: cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and time to peak (TTP). Perfusion values were measured in standard regions of interest (ROIs). ROIs were drawn in the cortical and subcortical flow territories of the anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral artery (PCA) and in the basal ganglia using in-house developed software (®MevisLab, software for medical image processing and visualization; http://www.mevislab.de) (Figure 2.1). Absolute mean perfusion values were determined for each ROI for each patient. For CBF and CBV, the ROI with the minimal value and; for MTT and TTP, the ROI with the maximal perfusion value was selected per patient.

Neuropsychological examination

The neuropsychological examination consisted of 11 subtests covering four main cognitive domains: memory, executive functioning, attention, and visuospatial functioning. Memory was assessed by the Digit Span backward of the Wechsler Adult Intelligence Scale III (WAIS-III), the immediate recall, delayed recall and recognition scores of the Rey Auditory Verbal Learning Task-Dutch version (RAVLT-D), the delayed Rey–Osterrieth Complex Figure Test (Rey-CFT) and Category Fluency (using animals). Executive functioning was measured using the Brixton Spatial Anticipation Test and the Letter Fluency (using 'N' and 'A'). The Digit Span forward of the WAIS-III and the Stroop Color Word Test were administered to measure attention. To evaluate visuospatial functioning and -construction, we used the copy score of the Rey-CFT.

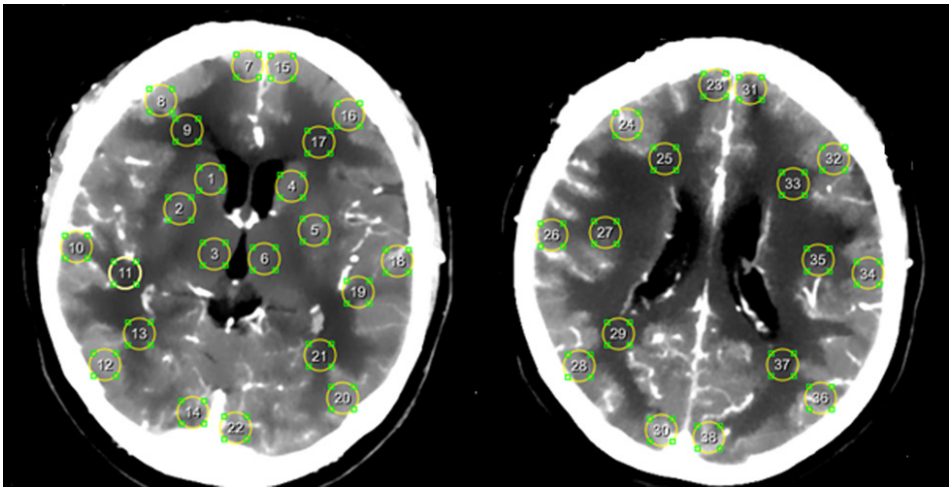

Figure 2.1 Standard ROIs in the cortical and subcortical flow territories of the anterior cerebral artery, middle cerebral artery and posterior cerebral artery and in the basal ganglia. Left: standard ROIs on the level of the thalamus and basal ganglia; right: standard ROIs on the level just cranial to the basal ganglia.

Raw test scores from the individual tests were transformed into *z*-scores based on the means and standard deviations of a control group containing 62 subjects with a mean age of 57.8 (58% women). Test scores are classified as mild deficit if between 1.5 and 2 standard deviations below the control mean and severe deficit if more than 2 standard deviations from the control mean. For an indication of global cognitive functioning, *z*-scores of all tests were summarized by a mean score.

Other possible determinants of cognition

For each patient, we collected the following variables: age, sex, educational level [using a Dutch classification system ranging from 1 (did not complete primary school) to 7 (university degree)],[8] method of aneurysm treatment (clipping or endovascular), and occurrence of non-acute neurological complications between CTP and discharge from hospital. Non-acute complications were dichotomized in ≥1 complication(s) and no complications. Rebleeding was defined as a sudden clinical deterioration with signs of increased hemorrhage on CT scan compared with previous CT imaging, or a sudden clinical deterioration suspect for rebleeding with fresh blood in the ventricular drain in which no CT scan was obtained. Delayed cerebral ischemia (DCI) was defined as a clinical deterioration (new focal deficit, decreased Glasgow Coma Scale of at least two points on the total score or one of its individual components, or both) lasting 1 hour or longer with no evidence for rebleeding or hydrocephalus on CT and no other medical explanation, such as cardiovascular or pulmonary complications, infections or metabolic disturbances.[9] Subacute hydrocephalus was determined as a bicaudate index

above the 95th percentile for age[10] and ≥20% increase with respect to the admission CTP. Procedure-related ischemia was defined as ischemia in the neurosurgical trajectory or in the trajectory of an external ventricular drain. Asymptomatic infarction was defined as ischemia seen on follow-up imaging that was not present on imaging on admission and was not accompanied by clinical symptoms. Bacterial meningitis was defined as fever in combination with a positive cerebrospinal fluid culture.

Power analysis
To find an effect size of 0.15 (small effect according to Cohen's classification) with a number of 71 patients and an alpha of 0.05 in a regression analysis of both 3 and 4 predictors (as we did in our analyses) we had a power of 0.8, which can be seen as a good.

Analyses
The relationship between CTP parameters (CBF, CBV, MTT and TTP) and cognitive functioning was analyzed using univariable linear regression analyses. Additionally, adjustments were (simultaneously) made for the three factors that had most influence on the regression coefficient, as well as for the four factors that affected the regression coefficient between CTP parameters and cognitive functioning most. Analyses were checked for collinearity. We considered a p-value <0.05 as statistically significant.

RESULTS

We included 71 patients. At the time of their visit to the outpatient clinic, 62 patients (87%) were living at home and 9 (13%) resided temporarily in a rehabilitation institution. Seventy patients (99%) were reasonably or completely functionally independent (Barthel Index 17–20). Characteristics of the included patients are listed in Table 2.1. The results of CTP imaging are shown in Table 2.2.

Neuropsychological examination
The Rey-CFT (copy and delayed recall) was not administered in five patients because of visual problems (n=3) and hemiparesis (n=2). In addition, some patients did not complete all neuropsychological tests within the available time resulting in missing delayed Rey-CFT scores (n=2), Brixton Spatial Anticipation Test scores (n=4), and Stroop Color Word Test scores (n=12). The mean z-score of global cognitive functioning was -0.43 (range -1.75 to 0.73). Results of the separate cognitive tests

are shown in Table 2.3. Twenty patients (28%) had severe cognitive deficits and 37 patients (52%) had mild cognitive deficits on one or more neuropsychological tests. The proportions of patients with cognitive deficits across the different domains were, with the exception of the domain attention, comparable (15–20%).

Analyses

In the univariable regression analyses TTP (B = -0.042, 95% CI -0.076 to -0.008) but no other CTP parameter was associated with cognitive functioning after aSAH. Adjustment for the level of education, treatment and non-acute complications did not influence the relationship between TTP and cognition. However, when age was added to the model, the relationship between TTP and cognition was no longer significant (Table 2.4).

Table 2.1 Characteristics of the 71 included aSAH patients.

Demographic characteristics	n	(%)
Women	60	85
Mean age in years (SD)	53	11
Education level (Verhage)		
Low (1-5)	58	82
High (6-7)	13	18
aSAH characteristics		
Admission WFNS score		
I	40	56
II	16	23
III	5	7
IV	5	7
V	5	7
Aneurysm location		
Internal carotid artery	3	4
Anterior communicating and cerebral arteries	31	44
Middle cerebral artery	13	18
Posterior communicating artery	15	21
Vertebrobasilar circulation*	9	13
Treatment received		
Clipping	22	31
Coiling	49	69
Acute complications		
Acute hydrocephalus	7	10
Intraparenchymal haemorrhage	14	20
Non-acute complications		
Rebleeding	1	1
Delayed cerebral ischemia	12	17
Subacute hydrocephalus	5	7
Procedure-related or asymptomatic ischemia	13	18
Bacterial meningitis	1	1
Mean follow up time after aSAH in weeks (SD)	11.4	4.5

aSAH = aneurysmal subarachnoid haemorrhage; n = number; % = percentage; SD = standard deviation; WFNS = World Federation of Neurosurgeons. * Including the vertebral artery, basilar artery, cerebellar arteries and posterior cerebral artery.

Table 2.2 CT perfusion values.

	Lowest perfusion value (SD)*	Mean perfusion value (SD)
CBF (mL/100 g/min)	14.5 (5.5)	34.5 (9.1)
CBV (mL/100 g)	1.1 (0.3)	2.0 (0.6)
MTT (s)	10.5 (1.3)	8.2 (0.9)
TTP (s)	18.6 (3.9)	16.2 (3.2)

SD = standard deviation; CBF = cerebral blood flow; CBV = cerebral blood volume; MTT = mean transit time; TTP = time to peak. * Lowest perfusion value: minimal value for CBF and CBV and maximal value for MTT and TTP.

Table 2.3 Performance on neuropsychological tests.

	Neuropsychological tests	n	Mild deficit n (%)	Severe deficit n (%)	Total deficits n (%)
Memory					
	Digit Span backward	71	1 (1)	0 (0)	1 (1)
	RAVLT-immediate recall	71	6 (8)	3 (4)	9 (13)
	RAVLT-delayed recall	71	12 (17)	7 (10)	19 (27)
	RAVLT-recognition	70	5 (7)	9 (13)	14 (20)
	Rey CFT-delayed recall	62	12 (19)	2 (3)	14 (23)
	Category Fluency	71	6 (8)	1 (1)	7 (10)
Executive functioning					
	Brixton Spatial Anticipation Test	67	2 (3)	3 (4)	5 (7)
	Letter Fluency	71	15 (21)	1 (1)	16 (23)
Attention					
	Digit Span forward	71	5 (7)	0 (0)	5 (7)
	Stroop Colour Word Test	59	0 (0)	1 (2)	1 (2)
Visuospatial functioning					
	Rey CFT-copy	65	6 (9)	8 (12)	14 (22)

n = number; % = percentage; RAVLT = Rey Auditory Verbal Learning Task; Rey CFT = Rey-Osterrieth Complex Figure Test.

Table 2.4 Relationship between perfusion and cognitive functioning.

	Min CBF		Min CBV		Max MTT		Max TTP	
	B	95% CI	B	95% CI	B	95% CI	B	95% CI
Unadjusted	0.001	-0.008 to 0.010	-0.043	-0.506 to 0.419	-0.043	-0.149 to 0.064	-0.042	-0.076 to -0.008
Sex	0.001	-0.008 to 0.010	-0.056	-0.526 to 0.414	-0.040	-0.149 to 0.068	-0.042	-0.077 to -0.007
Age	0.001	-0.007 to 0.009	-0.028	-0.461 to 0.405	-0.016	-0.118 to 0.085	-0.027	-0.062 to 0.008
Level of education	0.002	-0.007 to 0.011	0.000	-0.462 to 0461	-0.038	-0.144 to 0.067	-0.045	-0.079 to -0.011
Treatment	0.002	-0.007 to 0.011	-0.015	-0.485 to 0.456	-0.046	-0.153 to 0.061	-0.043	-0.077 to -0.008
Non-acute complications	0.001	-0.008 to 0.010	-0.018	-0.482 to 0.446	-0.032	-0.141 to 0.077	-0.041	-0.076 to -0.007
3 factors*	0.003	-0.006 to 0.012	0.036	-0.436 to 0.508	-0.043	-0.144 to 0.075	-0.045	-0.079 to -0.011
4 factors†	0.003	-0.005 to 0.011	0.050	-0.391 to 0.492	-0.008	-0.112 to 0.096	-0.030	-0.065 to 0.004

Min = minimal; CBF = cerebral blood flow; CBV = cerebral blood volume; Max = maximal; MTT = mean transit time; TTP = time to peak; B = unstandardized regression coefficient; 95% CI = 95% confidence interval; *Adjustment for level of education, treatment and non-acute complications; †Adjustment for level of education, treatment, non-acute complications and age.

DISCUSSION

We found no relationship between cerebral perfusion assessed within 24 hours after aSAH and cognitive outcome after 3 months. Although there was an association between TTP and cognitive outcome in a univariable analysis, multivariable analysis showed that this association was age dependent.

To our knowledge, no other studies have investigated the relationship between perfusion measured with CTP and cognitive outcome in patients with aSAH. In a study on perfusion heterogeneity measured with single-photon emission computed tomography (SPECT) made before aneurysm treatment and clinical outcome 1 year after aSAH, a relationship between perfusion heterogeneity, which determines the variation in perfusion, and executive functioning was found.[11] However, in contrast to our study, no corrections were made for confounders such as age.

In recent years, there is increasing interest in early brain injury after aSAH. Many factors contribute to brain injury in the acute phase, such as increased intracranial pressure, microvascular alterations in the basal lamina, platelet aggregation, acute vasospasm and reperfusion injury.[12-16] We hypothesized that perfusion deficits related to early brain injury affect cognition. Since no relationship between reduced cerebral perfusion within the initial 24 hours after aSAH and cognitive outcome in longer term was found in this study, the cause of the cognitive deficits after an aSAH is still not understood. The previously reported associations between the initial conditions of the patient on admission with the development of cognitive deficits[1,3-5] explain only a part of the cognitive deficits. As suggested in a previous review,[1] non-acute complications occurring during the clinical course may also play a role in cognitive deficits after aSAH. Therefore, in our analyses we adjusted for non-acute complications such as rebleeding, delayed cerebral ischemia, non-acute hydrocephalus, procedure related or asymptomatic ischemia, and meningitis. We were, however, not able to include all these complications as different dependent variables because of a lack of power and dispersion. Using a grouped-dependent variable for the non-acute complications could underestimate a potential association.

Besides the use of non-acute complications as one grouped variable, other potential limitations of our study need further explanation. First, we included patients with a CTP up to 24 hours after ictus. Since the peak in intracranial pressure and corresponding dip in cerebral blood flow might be most clear in the first minutes after aSAH,[17] we cannot exclude that impaired cerebral perfusion within the first hour after ictus is associated with cognitive deficits after SAH. However, since most aSAH patients cannot be scanned within 1 hour after ictus, it is impossible to collect data on ultra-early CTP in a large series of

patients. Second, since we included patients who were able to visit the SAH outpatient clinic, we only investigated patients with a relatively good recovery. Although the deficits in the overall cognitive score in aSAH patients are relatively subtle, an overall decrease in the scores is seen compared to the control group. Moreover, on separate neuropsychological tests almost one-third of the patients showed severe cognitive deficits and more than half of the patients had mild cognitive deficits in one or more tests. Thus, we assume that the lack of association between cognition and perfusion is not caused by selecting a group of patients with no or only minor cognitive deficits. Our sample is the group of patients who make a physically good recovery, but are hampered in daily life because of cognitive deficits. Finally, in this study, patients were scanned at the time of clinical deterioration. At that time often no infarctions were visible yet on CT. No CT imaging was done before hospital discharge or at a standard time, for example, 6 weeks after SAH. Therefore, in our regression analyses we adjusted for clinical deterioration due to DCI instead of (volume of) cerebral infarction due to DCI. Since areas with perfusion deficits were widespread and not confined to specific regions, no adjustments were made for location of the affected brain tissue. In addition, only the ROI with the maximum or minimum value depending on the perfusion map was used in our analysis. We did not take into account the number of ROIs with abnormal perfusion.

CONCLUSION

Perfusion in the initial 24 hours after aSAH does not explain the neuropsychological deficits 3 months after SAH. This lack of association might be explained by the delay between onset of aSAH and CTP, whereas the sharpest reduction in cerebral perfusion occurs during and directly following the hemorrhage. CTP assessment within the first minutes after aSAH, however, is impossible in large series of patients.

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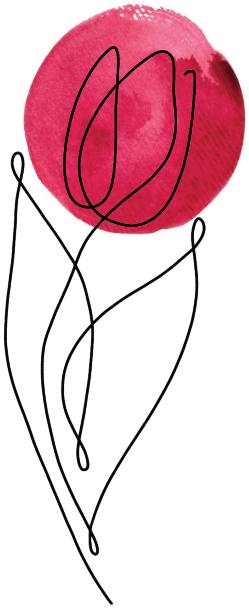
CHAPTER 3

The relationship between cerebral ischemia and cognitive outcome after aneurysmal subarachnoid hemorrhage



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ABSTRACT

Introduction

Cerebral ischemia is thought to be an important determinant of cognitive outcome after aneurysmal subarachnoid hemorrhage (aSAH), but the exact relationship is unclear. We studied the effect of ischemic lesions during clinical course on cognitive outcome 3 months after aSAH.

Methods

We studied 74 consecutive patients admitted to the University Medical Center Utrecht who had MRI post-coiling (3-21 days post-aSAH) and neuropsychological examination at 3 months. Ischemia was defined as hyperintensity on T2-FLAIR and DWI images. We measured both cognitive complaints (subjective) and cognitive functioning (objective). The relationship between cerebral ischemia and cognitive outcome was analyzed by logistic regression analyses.

Results

In 40 of 74 patients (54%) 152 ischemic lesions were found. The median number of lesions per patient was 2 (1-37) and the median lesion volume was 1.6 (<0.1-17.4) mL. No difference was found between the group with and the group without ischemic lesions with respect to the level of cognitive complaints. In the group with cerebral ischemia significantly more patients (55%) showed poor cognitive functioning compared to the group without cerebral ischemia (26%), (OR 3.4, 95% CI 1.3 to 9.1). We found no relationship between the number and volume of the ischemic lesions and cognitive functioning.

Conclusions

Cerebral ischemia detected on MRI during clinical course after aSAH is a marker for poor cognitive functioning 3 months after aSAH, irrespective of the number or volume of the ischemic lesions. If during clinical course after aSAH ischemic lesions are present on MRI, clinicians should consider neuropsychological assessment and cognitive rehabilitation.

INTRODUCTION

Patients who survive an episode of aneurysmal subarachnoid hemorrhage (aSAH) often show good physical recovery, but many have cognitive complaints or impairments that hamper complex activities in daily life, such as work and social participation.[1-4]

Cerebral ischemia plays a role in poor cognitive outcome after aSAH.[5-7] Besides hypoperfusion during aneurysmal rupture,[8] cerebral ischemia can also be a result of treatment of the aneurysm[9] or delayed cerebral ischemia (DCI).[10] Most previous studies on the relationship between cerebral ischemia and cognition after aSAH tried to distinguish cerebral ischemia due to the initial aSAH from delayed cerebral ischemia (DCI) and therefore focused on cerebral ischemia in the acute phase (<72 or <96 hours)[11,12] or in late (chronic) phase.[3,11,13-15] Moreover, these studies only included cognitive functioning and left out patient's own (subjective) experience about their cognitive abilities. As a result, the exact relationship between cerebral ischemia and cognitive outcome is not completely clear.

Insight in the relationship between cerebral ischemia (regardless of its underlying etiology) and cognition, might help predict patients' cognitive outcome after aSAH and help clinicians to decide if a neuropsychological assessment and cognitive rehabilitation are indicated. The aim of the present study is to examine whether aSAH patients with cerebral ischemia have an increased risk of poor cognitive outcome.

METHODS

aSAH patients

This study was approved by the Medical Ethics Review Committee of the University Medical Center of Utrecht (UMCU). Patients were retrieved from a prospectively collected series of aSAH patients admitted to the UMCU between November 2012 and February 2016 and, as part of a study protocol, had MRI between coiling and discharge. In the UMCU all patients discharged home or to a rehabilitation institution are invited for our routine outpatient clinic 3 months post-aSAH. At this outpatient clinic, a nurse-practitioner specialized in SAH asked patients about their cognitive complaints (questionnaire) and a trained neuropsychologist examined a neuropsychological examination (NPE). Inclusion criteria were: (1) SAH, defined as the presence of subarachnoid blood as shown by CT or lumbar puncture; (2) Aneurysmal cause of the SAH as determined by the visualization of an aneurysm on either CT angiography, magnetic resonance angiography (MRA), or digital subtraction angiography; (3) MRI performed between coiling and discharge and (4) patient's visit to the outpatient clinic 3 months post-aSAH.

Demographics and aSAH characteristics

Demographic data included sex, age and level of education. The level of education was classified using a Dutch classification system ranging from 1 [did not complete primary school] to 7 [university degree].[16] The aSAH characteristics were: (1) clinical condition on admission and (2) location of the aneurysm. The clinical condition on admission was graded using the Prognosis on Admission after Aneurysmal Subarachnoid Hemorrhage (PAASH).[17] A PAASH rating of I-III (Glasgow Coma Scale score 8-15) was classified as good clinical condition and a PAASH rating of IV-V (Glasgow Coma Scale score 3-7) as poor clinical condition.

Radiological characteristics

The amount of subarachnoid blood was rated on the diagnostic computed tomography (CT) scan (i.e. the first CT scan after ictus) by J.B.D.V. (3 years of experience with CT imaging) using the Hijdra score.[18] MRI was performed at either a 1.5T or a 3T scanner (Intera/Achieva, Philips Medical Systems, Best, The Netherlands) with a quadrature body coil for transmission and an eight-channel head coil as a signal receiver. The MR imaging protocol included a T1- and T_2- weighted imaging sequence, a time-of-flight MR angiography, a T_2-weighted fluid-attenuated inversion recovery (T_2-FLAIR) sequence and a diffusion-weighted imaging (DWI) sequence. The scan parameters of the T_2-FLAIR sequence were; TR/TI/TE= 10000/2800/140 and 10000/2800/120 ms, voxel size 0.7x0.7x5 mm^3 and 0.4x0.4x4 mm^3, and slice gap 1 mm. The scan parameters of the DWI sequence were; TR/TE=3348/98 and 3015/68 ms, b-factors = 2 (0 and 1000 s/mm^2), voxel size=1x1x5 mm^3 and 0.5x0.5x4 mm^3, and a slice gap of 1 mm. Ischemic brain lesions were defined as hyperintensity on the T_2-FLAIR and DWI. The T_2-FLAIR and DWI image quality, number of ischemic brain lesions and lesion location were evaluated simultaneously by a neuroradiologist (T.D.W., 30 years of experience with neuroradiology), who was blinded for the patients' information. The volume of the ischemic brain lesions was measured through manual segmentation on either the FLAIR or DWI images by M.E.H., also blinded for patients' information, using Picture Archiving and Communication System (PACS) software (Sectra AB, Linköping, SWEDEN).

Cognitive outcome

Cognitive outcome was measured both as cognitive complaints (subjective) and as cognitive functioning (objective). Cognitive complaints were identified using the 13 cognitive items of the Checklist for Cognitive and Emotional Consequences following stroke (CLCE-24).[19] Based on patient's answers on the interview at the SAH outpatient clinic, the interviewer scored a '0' for absence and a '1' per item for presence of complaints; the sum score indicates the number of experienced complaints.

Cognitive functioning was measured using a neuropsychological examination consisting of 13 (sub)tests covering six main cognitive domains: language, memory, attention, executive functioning, processing speed and visuospatial functioning. A shortened (15-item) version of the Boston Naming Test (BNT) was used to evaluate language. Memory was assessed by the Digit Span of the Wechsler Adult Intelligence Scale III (WAIS-III), the immediate recall and delayed recall scores of the Rey Auditory Verbal Learning Task-Dutch version (RAVLT-D), the delayed Rey-Osterrieth Complex Figure Test (Rey-CFT) and Category Fluency (using animals). A shortened version of the Visual Elevator subtest of the Test of Everyday Attention (TEA) was administered to measure attention. Executive functioning was measured using the Letter Fluency ('A'), Key Search of the Behavioral Assessment of Dysexecutive Syndrome (BADS) and the go/no go subtest of the Frontal Assessment Battery (FAB). Processing speed was assessed using the Digit Symbol Coding of the WAIS-III. To evaluate visuospatial functioning, we used Judgement of Line Orientation Test (JLO) and the copy score of the Rey-CFT.

Analyses

The number of cognitive complaints was dichotomized, based on the median split of the sum score of the CLCE-24 (3 cognitive complaints). Raw test scores from the individual neuropsychological tests were transformed into percentile scores based on norm scores of each test. If applicable corrections were made based on sex, age and/or level of education. Scores below the 5th percentile were considered as impaired. Next, the number of impaired tests per individual was determined and dichotomized based on the median split (2 impaired test scores). Descriptive analyses were used to describe baseline and imaging characteristics. The relationship between ischemic brain lesions (presence, number, volume) and cognitive complaints as well as the relationship between ischemic brain lesions (presence, number, volume) and cognitive functioning was investigated by logistic regression analysis. Because the clinical condition on admission after aSAH is related to cerebral circulation in the acute phase after aSAH[8], no adjustment for clinical condition on admission was made. Analyses were checked for collinearity. We considered a p-value <0.05 as statistically significant.

RESULTS

aSAH population

Ninety-four patients were eligible for inclusion in this study. Of these 94 patients, 20 patients did not complete the NPE because of pain (1), fatigue (1), emotionality during the assessment (2), insufficient proficiency of Dutch language (3), aphasia (2), lack of motivation (2) or lack of time (5). The remaining 74 patients were included in the analyses. Characteristic of the included patients are listed in table 3.1.

Ischemic brain lesions

In 40 of 74 patients (54%) 152 ischemic lesions were found, of which 4 were old lesions (before aSAH). In the subgroup of 40 patients with ischemic lesions, the mean number of lesions per patient was 4 (median 2, range 1-37) and the mean lesion volume was 1.6 mL (median 0.2, range <0.1 to 17.4). The location of the cerebral ischemia is shown in Table 3.1.

Cognitive outcome

Sixty-one patients (82%) reported at least one cognitive complaint. The frequencies of the different cognitive complaints are shown in table 3.2. Regarding the NPE, nine patients (12%) showed no impaired test scores. Thirty-four patients (46%) had impairments ($\leq 5^{th}$ percentile) on one or two of the subtests. Forty-nine patients (42%) were impaired on more than two subtests of the NPE. Results of the separate cognitive tests are shown in Table 3.3.

Relationship ischemic parameters and cognitive outcome

Neither presence of ischemic lesions (OR 1.46, 95% CI .58 to 3,70), nor the number (OR 1.12, 95% CI 0.92 to 1.16) or volume of the ischemic lesions (OR 1.00, 95% CI 1.00 to 1.00) were significantly related to the level of cognitive complaints. Of the 40 patients with ischemic lesions, 22 (55%) had poor cognitive functioning, whereas in the 34 patients without ischemic lesions 9 patients (26%) had poor cognitive functioning (OR 3.40, 95% CI 1.27 to 9.08). Within the subgroup of patients with ischemic brain lesions, the number (OR 1.03, 95% CI .91 to 1.17) and volume (OR 1.00, 95% CI 1.00 to 1.00) of the ischemic lesions were not related to cognitive functioning.

Table 3.1 Characteristics of aSAH patients (n=74).

Demographic characteristics	n	(%)
Sex		
Female	57	77
Age at time of bleeding (mean, SD)	56 (±10) yrs	
Level of Education		
Low (Verhage 1-3)	12	16
Middle (Verhage 4-5)	46	62
High (Verhage 6-7)	16	22
Clinical characteristics		
Time between MRI and aSAH (days; mean, range)	12 (3-21)	
Time between aSAH and NPE (days; mean, range)	60 (24-109) days	
Clinical condition on admission (PAASH)		
Good		
I = GCS 15	44	60
II = GCS 11- 14	26	35
III = GCS 8- 10	1	1

Table 3.1 Continued.

Clinical characteristics (Continued)	n	(%)
Clinical condition on admission (PAASH) (Continued)		
Poor		
IV = GCS 4- 7	1	1
V = GCS 3	2	3
Imaging characteristics		
Amount of subarachnoid blood (Hijdra score) (Median, range)		
Blood in basal cisterns	24 (0-30)	
Blood in ventricles	2 (0-9)	
Total	26 (0-39)	
Aneurysm location		
Anterior circulation		
Acom /A1 / pericallosal artery	41	55
MCA	0	0
ICA/Pcom	23	31
Posterior circulation		
PCA	1	1
Basilar artery	7	9
Vertebral arteries / PICA / AICA	2	3
Location cerebral ischemia		
Left	14	19
Right	14	19
Both	12	16
Anatomical areas (number and % of all ischemic lesions)		
Cortical	76	50
Subcortical	61	40
Internal capsule	5	3
Basal ganglia	6	4
Cerebellum	4	3
Brainstem	0	0
Perfusion territories (number and % of ischemic lesions)		
ACA	26	17
MCA	32	21
PCA	10	7
Basilar artery, vertebral artery and PICA	7	5
Watershed areas	77	51

aSAH = Aneurysmal Subarachnoid Haemorrhage; MRI = Magnetic Resonance Imaging; NPE = Neuropsychological Examination; PAASH = prognosis on admission of aneurysmal subarachnoid haemorrhage; GCS, Glasgow Coma Scale; Acom = Anterior Communicating Artery; MCA = Middle Cerebral Artery; ICA = Internal Carotid Artery; Pcom = Posterior Communicating Artery; PCA = Posterior Cerebral Artery; PICA = Posterior Inferior Cerebellar Artery; AICA = Anterior Inferior Cerebellar Artery; ACA = Anterior Cerebral Artery.

Table 3.2 Frequencies of cognitive complaints (CLCE-24).

	n	%
Keeping up; has become slower	46	62
Attending to things	42	57
Remembering new information	40	54
Doing two things at once	31	42
Planning and organizing things	23	31
Taking initiative	20	28
Performing daily activities	20	28
Remembering old information	6	8
Perceiving time	5	7
Orientating to places or persons	3	4
Speaking or writing	1	1
Social aspects of language	1	1
Attending to a part of the body or space	1	1

Table 3.3 Frequencies of impaired test scores on neuropsychological examination.

Cognitive domain	Test	Impaired test score (<5th percentile)					
		Ischaemic lesions (n=40)		No ischaemic lesions (n=34)		Total (n=74)	
		n	%	n	%	n	%
Language	BNT	12	30	4	12	16	22
Memory	Digit Span	6	15	5	15	11	15
	RAVLT direct	17	43	9	27	26	35
	RAVLT delayed	18	45	10	29	28	38
	Rey-CFT delayed	8	20	3	9	11	15
	Category Fluency	3	8	0	0	3	4
Attention & Executive	Visual elevator score	6	15	4	12	10	14
functioning	Visual elevator time	9	23	6	18	15	20
	Letter Fluency	8	20	4	12	12	16
	Key Search	6	15	5	15	11	15
	Go-No go	6	15	8	24	14	19
Processing speed	Digit Symbol Coding	5	13	3	9	8	11
Visuospatial functioning	JLO	4	10	5	15	9	12
	Rey-CFT copy	9	23	7	21	16	22

BNT = Boston Naming Test; RAVLT = Rey Auditory Verbal Learning Task; Rey-CFT = Rey-Osterrieth Complex Figure Test; JLO = Judgment of Line Orientation.

DISCUSSION

In aSAH patients with relatively good functional outcome, those with cerebral ischemia have an increased risk of poor cognitive functioning, compared to those without cerebral ischemia. Although the presence of cerebral ischemia was clearly related to cognitive functioning, within the group of patients with cerebral ischemia there was no relation between the number and volume of ischemic lesions and cognitive functioning.

The absence of a relationship between the number and volume of ischemic lesions and cognitive functioning is in line with the findings of the only previous study we found to the relationship between ischemic lesions and cognitive functioning using number and volume of ischemic lesions in their analyses.[12] In a study that examined infarct load after aSAH by the number of regions in which cerebral ischemia was located, the number of regions involved, was related to cognitive functioning.[5] Although that study only focused on DCI, this suggests that not the number or volume of the ischemic lesions, but the distribution of the ischemic lesions is an important factor of the variability in cognitive functioning after aSAH.

The lack of a relationship between the number and volume of the ischemic lesions and cognitive functioning after aSAH in our study, might also be a result of the relative low ischemic load found in our sample, which is possibly a consequence of the selection of patients in our study. Although MRI is more sensitive in detecting cerebral ischemia after aSAH than CT,[20] the use of MRI has led to a selection of relatively good patients, since MRI is not always feasible in patients with a poor clinical condition. Moreover, we only included patients who were discharged home or to rehabilitation center with intention to be transferred home in 3 months. Although patients in our sample had a relatively good functional outcome, they did experience considerably cognitive complaints and cognitive impairments. Despite the relatively low ischemic load, we found an effect of ischemia on cognitive functioning, indicating a robust relationship.

Because of limited power in our sample, we did not perform a subgroup analysis on the location of ischemic lesions. The location of the ischemic lesions might however be important for the nature and severity of the cognitive impairments. Small brain lesions can disturb hubs and reduce the integrity of functional brain networks which is related to cognitive decline.[21] Moreover, our study cannot give any judgement about the etiology of the ischemic lesions that are found, because of variance in the timing of the post-SAH MRI and the absence of a pre-aSAH MRI.

In contrast to cognitive functioning, we found no relation between cerebral ischemia and cognitive complaints after aSAH. This discrepancy confirms that this subjective measure of cognition reflects another construct compared to objective measures of cognitive outcome. Only a small proportion of the cognitive complaints can be explained by potentially underlying cognitive impairments.[1]

Based on the present study, clinicians should consider referral for a neuropsychological examination and cognitive rehabilitation when during clinical course after aSAH one or more ischemic lesions are present on MRI. Network or connectivity studies are needed to better understand the relationship between location of the cerebral ischemia and cognitive functioning. Future studies on the effectiveness of interventions to prevent cerebral ischemia after aSAH should not only focus on functional outcome but also take effects on cognitive outcome into account.

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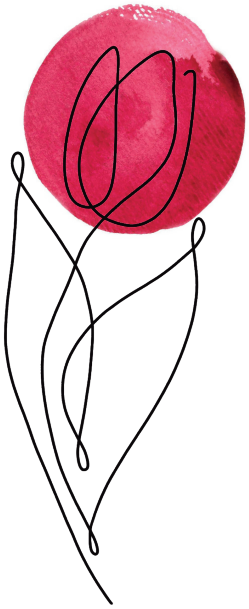
CHAPTER 4

Effect of magnesium on cognition after aneurysmal subarachnoid hemorrhage in a randomized trial



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ABSTRACT

Introduction

In randomized trials magnesium supplementation did not improve clinical outcome after aneurysmal subarachnoid hemorrhage (aSAH) on handicap scales. After aSAH, many patients have cognitive problems that may not translate into handicap. The effect of magnesium on cognitive outcome after aSAH was studied.

Methods

In total, 209 patients who had been included in the Magnesium for Aneurysmal Subarachnoid Hemorrhage (MASH-2) trial in the University Medical Centre of Utrecht were studied. Patients had been randomized to 64 mmol magnesium sulfate daily or placebo during hospitalization. Three months after aSAH patients underwent a neuropsychological examination (NPE) consisting of six neuropsychological tests or a brief cognitive assessment. Poisson and linear regression analyses were used to analyze the effect of magnesium on cognition.

Results

In the magnesium group 53 (49.5%) of the 107 patients and in the placebo group 51 (50.0%) of the 102 patients scored lower than the median cognitive score (relative risk 0.99, 95% CI 0.76 to 1.30). Linear regression analyses showed no significant relationship between intervention and cognition (B = 0.05, 95% CI 0.15 to 0.33).

Conclusions

Treatment with magnesium has no effect on cognitive outcome after aSAH.

INTRODUCTION

Despite positive results from preclinical and phase II studies, large randomized clinical trials established that treatment with magnesium does not improve clinical outcome after aneurysmal subarachnoid hemorrhage (aSAH).[1,2] The outcome in these trials was assessed by means of handicap scales. However, cognitive problems often hamper aSAH survivors and may not be detected with handicap scales.[3] The aim of this study was to assess the effect of magnesium on cognition after aSAH.

METHODS

Study design and patients

Patients admitted in the University Medical Centre of Utrecht (UMCU) who had been included in the randomized controlled trial Magnesium for Aneurysmal Subarachnoid Hemorrhage (MASH-2, registered ISRCTN 68742385, EudraCT 2006-003523-36)[1] were studied. In the UMCU all patients discharged home or to a rehabilitation institution are invited for our routine outpatient clinic 3 months post-aSAH including neuropsychological examination (NPE). Patients in whom the aneurysm was not proven by computed tomography, magnetic resonance or conventional angiography and patients with more than 30% missing tests on the NPE were excluded. A part of the data in our study was derived from the MASH-2 trial which complies with the Declaration of Helsinki and good clinical practice guidelines. All patients provided written and oral informed consent for this trial. The use of the additional neuropsychological data in the present study was approved by the UMCU Medical Ethics Committee. These data were derived from a prospective data collection according to clinical care as usual; therefore, no additional informed consent was used.

MASH-2

In the double-blinded MASH-2 study patients were randomized to 64 mmol magnesium or a matching placebo (saline).[1] Treatment was started within 4 days after the aSAH and continued 20 days after hemorrhage onset, or until hospital discharge or death if it occurred sooner. Functional outcome was measured by the modified Rankin Scale (mRS) 3 months after the aSAH.

Neuropsychological examination

Between November 2006 and August 2008, the NPE consisted of six standard neuropsychological tests covering memory, attention, executive functioning and visuospatial functioning. From September 2008 to March 2011, the NPE protocol was changed into

a brief cognitive assessment. This assessment consisted of 18 items evaluating memory, language, attention, executive functioning, visuospatial functioning and orientation on a score ranging from 0 (unimpaired) to 2 (severely impaired). Overall cognitive functioning was measured with a sum score of all 18 items. (More information about both NPEs is presented in Supplementary File S4.1.

Analyses

Scores on both the NPE and the brief cognitive assessment were transformed into *z*-scores based on means and standard deviations of all patients per type of assessment. The *z*-scores of the individual tests of the NPE were summarized in a mean *z*-score to parallel the *z*-score of the brief cognitive assessment. The mean *z*-scores of both assessments were grouped into one overall *z*-score. Cognition was analyzed both as a continuous (overall *z*-score) and dichotomous variable (dichotomized by the median of the overall *z*-score). The effect of magnesium was assessed by comparing patients who received magnesium with those on placebo with linear and Poisson regression analyses. Moreover, a multiple regression analysis was performed including adjustments for other possible determinants of cognition that changed the magnitude of the B (linear regression) or relative risk (RR) (Poisson regression) by >5%. These determinants were age, sex, educational level [using the Dutch Verhage classification system ranging from 1 (did not complete primary school) to 7 (university degree)],[4] clinical condition on admission measured with the World Federation of Neurosurgeons SAH grading scale,[5] method of aneurysm treatment (clipping or endovascular) and the neurological complications delayed cerebral ischemia and hydrocephalus. Because there was only one patient with aneurysmal rebleeding, this neurological complication was not included as a possible determinant. After the multiple regression analyses, a subgroup analysis was performed according to the type of cognitive assessment.

RESULTS

In total, 209 patients were included (Figure 4.1); their baseline characteristics are listed in Table 4.1. The mean interval for the NPE was 12 weeks after aSAH.

Neuropsychological examination

Patients who performed the NPE did not differ substantially from patients who completed the brief cognitive assessment with respect to the distribution of the intervention and the demographic and aSAH characteristics (Table 4.1). For the distribution and median split of the *z*-scores of both NPEs see Supplementary File S4.2

Analyses

In the magnesium group 53 (49.5%) of the 107 patients and in the placebo group 51 (50.0%) of the 102 patients scored lower than the median cognitive score (RR = 0.99, 95% CI 0.76 to 1.30). No significant relationship was found between magnesium and cognition in the linear regression analyses (mean overall *z*-scores: magnesium group 0.05, placebo group -0.04, B = 0.09, 95% CI -0.15 to 0.33). Upon adjustment the RR estimate hardly changed whereas B was influenced by age (B = 0.05, 95% CI 0.18 to 0.28), level of education (B = 0.08, 95% CI 0.16 to 0.30), delayed cerebral ischemia (B = 0.08, 95% CI 0.15 to 0.31) and hydrocephalus (B = 0.11, 95% CI 0.12 to 0.35) yielding a multivariable estimate of 0.05, 95% CI -0.17 to 0.26. Subgroup analyses showed no differences between the effect of magnesium when analyzing patients with an NPE (B = -0.06, 95% CI 0.32 to 0.20; RR = 1.04, 95% CI 0.70 to 1.54) or the brief cognitive assessment (B = 0.11, 95% CI -0.23 to 0.44; RR = 0.98; 95% CI 0.67 to 1.43).

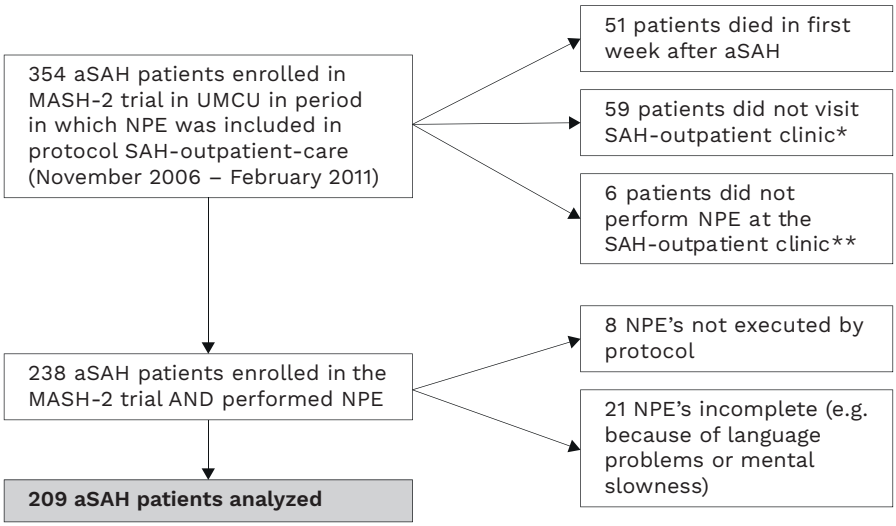

Figure 4.1 Patient inclusion.

MASH = Magnesium for aneurysmal subarachnoid haemorrhage; UMCU = University Medical Centre Utrecht; aSAH = Aneurysmal subarachnoid haemorrhage; NPE = Neuropsychological examination. *Reasons varied from being hospitalized, living abroad to no-show. **Because of visual problems, already performed NPE elsewhere or patient's refusal.

Table 4.1 Characteristics of aSAH patients (n=209).

	Magnesium (n=107)		Placebo (n =102)	
	n	(%)	n	(%)
Demographic Characteristics				
Women	84	(79)	81	(79)
Mean age in years (SD)	53.7 (11.7)		55.7 (11.5)	
Educational level				
Low-moderate (Verhage 1-5)[4]	82	(77)	81	(79)
aSAH characteristics				
WFNS				
I-III, GCS 13-15	92	(86)	87	(85)
Aneurysm treatment*				
Clipping	45	(42)	45	(44)
Coiling	61	(57)	57	(56)
Neurological complications				
Rebleeding	0	(0)	1	(1)
DCI	19	(18)	20	(20)
Hydrocephalus	21	(20)	16	(16)
Outcome 3 months after aSAH				
Poor functional outcome				
Slight/moderate disability (mRS 2-3)	45	(42)	46	(45)
Moderately/severe disability (mRS 4-5)	6	(6)	7	(7)
Cognitive outcome				
Median (Range) *z*-score cognitive outcome	0.1 (-3.0 – 1.3)		0.1 (-3.0 -1.2)	
Cognitive score lower than median	53	(50)	51	(50)

aSAH = Aneurysmal Subarachnoid Haemorrhage; WFNS = World Federation of Neurosurgeons; GCS = Glasgow Coma Score; DCI= delayed cerebral ischaemia; mRS = modified Rankin Scale; * One patient was not treated for a basilar top aneurysm, because both posterior cerebral arteries originated from this aneurysm and both carotid arteries were occluded.

DISCUSSION

Magnesium does not influence cognitive outcome after aSAH. To our knowledge this is the first study that used cognition as the outcome measure in a randomized trial of magnesium in aSAH patients. Patients were retrieved from the MASH-2 study,[1] which is the largest randomized controlled trial investigating magnesium in aSAH patients to date. Not all patients of the MASH-2 trial met the inclusion criteria of the current study but, given the criterion that patients had to be discharged home or to a rehabilitation institution, a large study population with relatively good outcome remained.

A limitation of our study is that two different measures of cognitive outcome were used. Cognitive data were derived from usual clinical care in which halfway through the study period a change was made from a formal NPE to a brief cognitive assessment. A subgroup analysis, however, showed no differences between the effects of magnesium when analyzing the two measures of cognitive outcome separately.

CONCLUSIONS

This study shows that magnesium has no effect on cognitive outcome after aSAH.

ACKNOWLEDGEMENTS

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SUPPLEMENTARY FILES

S4.1 Neuropsychological examinations

Supplement 4.1.1 Neuropsychological Examination

Cognitive Domain	Test
Memory	Digit span backward (WAIS III)
	Rey Auditory Verbal Learning Task (Dutch version)
	Rey-CFT delayed
	Category fluency (animals)
Attention	Digit span forward (WAIS III)
	Stroop Color Word Test
Executive functioning	Letter fluency ('N' and 'A')
	Brixton Spatial Anticipation Test
	Rey-CFT copy

WAIS III = Wechsler Adult Intelligence Scale III; Rey-CFT = Rey-Osterrieth Complex Figure Test

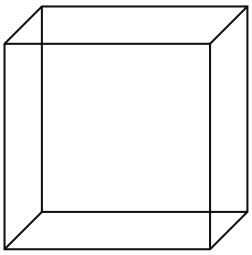
Supplement S4.1.2 Translation of the Dutch Brief Cognitive Assessment

Item 1	Observation voluntary speech (fluency, articulation, prosody, content)
Item 2	Can you tell me the months of the year backwards? (December, November, October, September, August, July, June, May, April, March, February, January)
Item 3	I am going to say a few words, repeat them when I am finished. (Breda, trumpet, purple, cat, friendship) (repeat the words if the participant does not repeat all 5 words correctly)
Item 4	I am going to put some coins in different places within this room. (put five coins in different places at different heights spread throughout the whole room) Can you tell me where the coins are?
Item 5	Put down a notepad, a pencil with a tip, a pencil without a tip and a toothbrush on the table. Can you draw a clock with all the hours on it and place the hands at ten past eleven?
Item 6	Copy this figure (see supplement S4.1.2.a). *Maximum time is 3 minutes.*
Item 7	Repeat the words I said earlier. (Breda, trumpet, purple, cat, friendship)
Item 8	Tell me again where the coins are.
Item 9	Tell me what you had for diner last night.
Item 10	Read this sentence aloud and do what it says (*see supplement 4.1.2.b*).

Supplement S4.1.2 Continued

Item 11	What is this? (point at three objects and two body parts) Which colour is this? (point at two objects with different colours) Can you tell me what I am referring to in the next sentence? (the object a referee uses when a foul is made, whistle) (It gnaws and builds dams in rivers, beaver)
Item 12 (A,B)	Put a white piece of paper on the table. Can you write down your name? Write down where we are at this moment and what day of the week it is.
Item 13	You have 1 minute to tell me as many words as you can think of that start with the letter A. You can say any word you think of as long as it is not a proper name. (So no first names, names of places or countries). *(maximum time is 1 minute)*
Item 14	You can see a figure here that is repeating itself. Can you continue this figure starting here, (point) till the edge of the paper without lifting your pencil? *(see supplement 4.1.2.c)*
Item 15	I am going to tell you a sequence of numbers and letters. There is a pattern. Can you try to continue this pattern? 1-A-2-B-3-… (C-4-D-5-E-6-F-7-G-8-H-9-I-10-J-11-K-12-L-13)
Item 16	I am going to read you a short story. You can read along *(see supplement 4.1.2.d)*. Pay attention. When I am ready I will ask you questions about the story. "I'm really hungry", said Els, "Will you watch on your side Rob? They drove on for another few minutes. "See, at the end of that side street", he said, "stop there." Where are Rob and Els? Where will Rob and Els stop? (by courtesy of A. van Loon-Vervoorn)
Item 17	Start here (point at the figure in the middle of the maze) and draw the way to the exit (point it) of the maze. (see supplement 4.1.2.e)

Supplement 4.1.2.a



Supplement 4.1.2.b

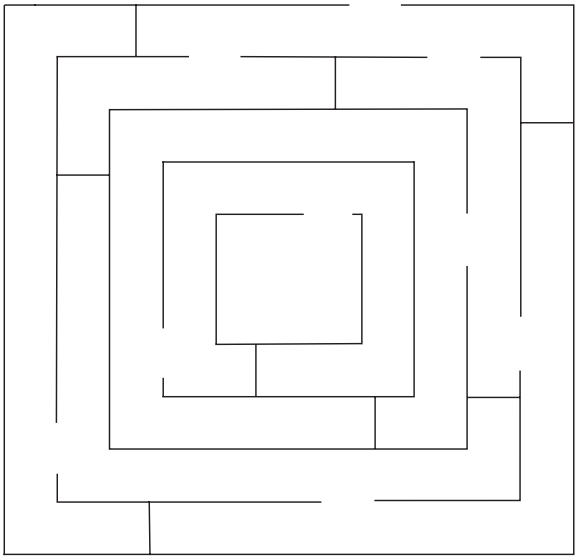
Show me how you hammer a nail in the table.
Close your eyes and touch your nose with your thumb.

Supplement 4.1.2.c

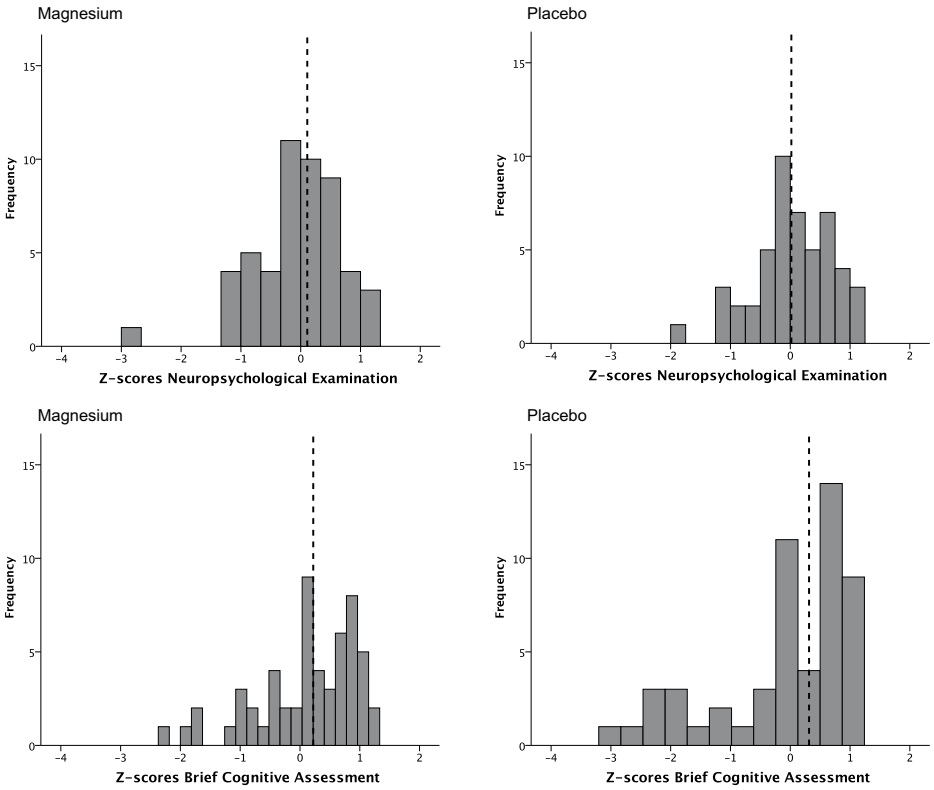
Supplement 4.1.2.d

"I'm really hungry", said Els, "Would you please watch on your side Rob?"
They drove on for another few minutes.
"See, at the end of that side street", he said, "stop there."

Supplement 4.1.2.e



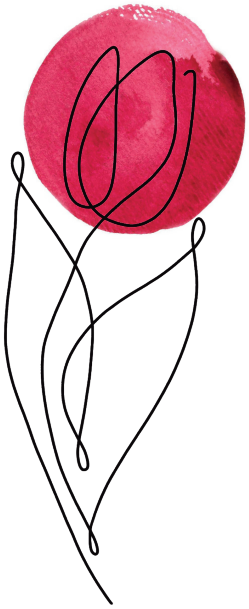
S4.2 Neuropsychological examinations: Distribution of cognitive scores



Supplement 4.2 Distribution and median split (dashed line) of test results (*z*-scores) of the Magnesium group and the placebo group on both the neuropsychological examination and the brief cognitive assessment.

CHAPTER 5

Ventricular volume in relation to cognitive outcome after aneurysmal subarachnoid hemorrhage



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ABSTRACT

Introduction

The cause of cognitive complaints and poor cognitive functioning after aneurysmal subarachnoid hemorrhage (aSAH) is unclear. Acute hydrocephalus might be an important determinant, especially for memory functions. We examined the relation between volume of the cerebral ventricles in the initial two weeks after aSAH and cognitive outcome (complaints and functioning) on follow up.

Methods

In this prospective cohort study, we included 109 consecutive aSAH patients who were interviewed with the Checklist for Cognitive and Emotional consequences following stroke (CLCE-24) and underwent a comprehensive neuropsychological examination 3 months after aSAH. Determinants were the largest volume on CT's within the first 14 days after aSAH for the entire ventricular system and for the temporal horns only. The relationship between the ventricular volumes and cognitive outcome was examined by linear and logistic regression analyses.

Results

Total ventricular volume was not related to overall cognitive complaints, but the volume of the temporal horns was related to memory complaints (B= 0.19, 95% CI 1.03 to 1.42, p=0.02). Moreover, we found no effect of total ventricular volume on cognitive functioning, but the volume of the temporal horns was related to the Rey-CFT-delay (incidental, visual memory) (B=-4.88, 95% CI -8.96 to -0.80, p=0.02).

Conclusion

On group level, volume of the temporal horns in the (sub)acute phase after aSAH has a small effect on both memory complaints and functioning. It is unlikely that aggressive drainage in patients with enlarged temporal horns but without clinical symptoms of hydrocephalus in the acute phase after aSAH will substantially decrease memory complaints and improve memory functioning.

INTRODUCTION

Many survivors of an aneurysmal subarachnoid hemorrhage (aSAH) who show good physical recovery, cannot regain their pre-morbid level of functioning. They often experience cognitive complaints and have persistent cognitive impairments which have a large impact on quality of life and on resuming work or (social) activities.[1-4]

The causes of these cognitive complaints and impairments are not yet completely understood, especially when in the chronic phase after aSAH no substantial lesions are visible on computerized tomography (CT) or magnetic resonance imaging (MRI). One of the factors that might contribute is an acute hydrocephalus after aSAH. Acute hydrocephalus is a frequent complication after aSAH that has a negative effect on cerebral perfusion in the acute phase, especially in the vicinity of the ventricles.[5] In almost half the patients, acute hydrocephalus recovers spontaneously,[6] however little is known about the residual impact after acute hydrocephalus.

Results on the relationship between acute hydrocephalus and cognitive functioning after aSAH are conflicting. Several studies found a negative effect of acute hydrocephalus on cognitive outcome, especially on memory functions.[7-9] This may be explained by hypoperfusion of the hippocampus from the enlarged temporal horn.[10] The hippocampus is involved not only in (associative) learning, but also retrieval of information from episodic memory.[11] There are however also studies that did not find a relation between hydrocephalus and cognitive outcome after aSAH.[12,13]

A reason for these conflicting results might be the differences in definition and measurement of acute hydrocephalus used in previous studies. In some of the studies hydrocephalus was defined by enlarged ventricles for which an external ventricular drainage (EVD) or ventriculoperitoneal shunt was necessary, while other studies used linear measurements such as the bicaudate index[14] or mean of temporal horn diameter. Linear measurements depend on the level of the brain CT scan image that is used and are often translated in a dichotomous measure (presence/absence of hydrocephalus). Interobserver variability of these linear measurements is substantial.[15] Volumetric measurements (continuous measurements) have the advantage that they are more accurate than linear measures, the entire ventricular system is used to assess ventricular size, and that components of the ventricular system can be determined and measured separately.

In the present study, we examined the effect of cerebral ventricular volume during the initial two weeks after aSAH on both cognitive complaints and functioning at 3 months in aSAH patients without any secondary neurological complications (e.g. rebleeding,

secondary ischemia or infarction, meningitis or delayed hydrocephalus). We also assessed the relation between the volume of the temporal horns specifically and memory (complaints and functions). If increased cerebral ventricular volume is indeed associated with poor cognitive outcome after aSAH, treatment of enlarged ventricles could be worthwhile, even in the absence of clinical symptoms of acute hydrocephalus.

METHODS

Procedure

We retrieved data from prospectively collected series of aSAH patients admitted to the University Medical Center Utrecht (UMCU) and visited our multidisciplinary SAH outpatient clinic 3 months after aSAH between November 2006 and September 2008 and between March 2011 and May 2012. In our institution all patients with aSAH routinely undergo CT on admission and during follow up. At the SAH outpatient clinic, SAH patients discharged home or to a rehabilitation institution undergo a neuropsychological examination (NPE) by a neuropsychologist 3 months after the aSAH. Inclusion criteria of the study were (1) 18 years of age or older; (2) SAH was caused by an aneurysm as proven by CT, MR or conventional angiography; (3) proficiency in the Dutch language. Exclusion criteria were (1) visit at the outpatient clinic in the period of October 2008 and February 2011, because during this period the NPE protocol was temporarily changed into a cognitive screening instrument. (2) Intraparenchymal or subdural extension of the hemorrhage. (3) Secondary neurological complications; rebleeding, secondary ischemia or infarction, meningitis and delayed hydrocephalus (>14 days after aSAH). (5) Other neurological diseases in medical history which causes cognitive deficits. The study was approved by the Medical Ethics Review Committee of the UMCU. Data was derived from a prospectively data-collection according to clinical-care-as-usual, therefore no informed consent was used.

Demographics and aSAH characteristics

Demographic data included sex, age and level of education. The level of education was classified using a Dutch classification system ranging from 1 [did not complete primary school] to 7 [university degree].[16] The aSAH characteristics were: (1) clinical condition on admission (2) location of the aneurysm and (3) treatment of the aneurysm (clipping versus endovascular). The Glasgow Coma Scale (GCS)[17] was used to measure the level of consciousness on admission and categorized based on the Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage (PAASH) grading scale.[18]

Ventricular volume

We measured the ventricular volumes on the CT scans that were performed between admission and the visit at the outpatient clinic 3 months post aSAH. Volumes were measured with the program Analyze software (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN, USA). In this program the ventricles and other cerebral spinal fluid (CSF) compartments were extracted from the brain by given thresholds (in Hounsfield units). Then, we separated the ventricles from other CSF compartments with semi-automatic and manual techniques, to calculate ventricular volume in milliliters (ml). For the analyses we used the largest ventricular volume after aSAH measured on CT's during the initial two weeks after the aSAH.

The volume of the temporal horns was measured on the scan with the largest total ventricular volume. The cranial cut-off point for the temporal horn on the axial cross section image was the transition of temporal horn to the wider trigone before the occipital horn was visible. Segmentation was performed by an investigator blinded for the results of cognitive data.

Cognitive outcome

Cognitive complaints were administered using the 13 cognitive items of the Checklist for Cognitive and Emotional Consequences following stroke (CLCE-24).[19] The interviewer scored a '0' for absence and a '1' for presence of complaints; the sum score indicates the number of experienced complaints.

The NPE consisted of a total of nine tests. In the domain 'memory' patients performed six tests tapping the various components of memory including verbal working memory assessed by the Backward Digit Span of the Wechsler Adult Intelligence Scale III (WAIS-III) and category fluency (semantic memory) using animal naming. The Dutch version of the Rey Auditory Verbal Learning Task (RAVLT) was used to measure verbal learning, revealing scores for immediate and delayed recall and recognition. Visual memory was evaluated using the delayed Rey-Osterrieth Complex Figure Test (CFT). Besides the visual component this task also reveals the automaticity of learning by its incidental component.[20] With respect to the domain 'attention', the Forward Digit Span of the WAIS III was examined. Phonological fluency was used as a concept generation test to assess 'executive functioning' and the copy score of the Rey-CFT for 'visuospatial functioning'.[21] In clinical care at the SAH outpatient clinic, the NPE protocol included additional tests that were different in the periods of 2006-2008 and 2011-1012 and were therefore excluded.

Analyses

Ventricular volume and cognitive complaints

To analyze the relationship between ventricular volume and cognitive complaints, both the total sum score of the CLCE-24 and the score on the two memory questions of the CLCE-24 were used. The relationship between the total ventricular volume and cognitive complaints (sum score CLCE-24) were examined by linear regression analyses. A logistic regression analysis was performed to the relationship between volume of the temporal horns and the presence of memory complaints (0 = no memory complaints, 1 = one or two memory complaints).

Ventricular volume and cognitive functioning

In order to describe the level of cognitive functioning (NPE) in terms of impairment, raw test scores from the individual neuropsychological tests were transformed into percentile scores based on published norm scores of each test. Scores ≤ 5th percentile were considered as impaired. To measure the relationship between ventricular volume and cognitive functioning we used raw test scores of each individual test. The relationship of both the total ventricular volume and the volume of the temporal horns with the different tests of the NPE were examined by linear regression analyses. If applicable, adjustments were (simultaneously) made for sex, age and level of education. Finally, in order to examine the effect of ventricular volume in the acute phase (within two days after aSAH), we performed a sensitivity analysis in which we excluded patients with the largest volume >2 days after aSAH (subacute). Analyses were checked for collinearity. A p-value <0.05 was considered as statistically significant.

RESULTS

aSAH population

The baseline characteristics of 109 included patients are listed in table 5.1.

Ventricular volume

In 85 of the 109 patients (78%) the ventricular volume was the largest within the first two days after aSAH. The mean volume of the largest ventricles of the 109 patients was 41.19 ml (range 7.55-120.56). The mean volume of the temporal horns of the ventricles was 3.45 ml (range .22-13.48).

Cognitive outcome

CLCE-24 scores were not available in 3 out of the 109 included patients. In the remaining 106 patients, 91 (84.8%) reported at least one cognitive complaint. "Becoming slower" (64.2%) and problems with "attending to things" (56.0%) were most reported cognitive complaints. Fifty-eight patients (53.2%) reported memory complaints in one or both memory questions of the CLCE-24. With respect to the NPE, 68 patients (62.4%) had impaired test scores (≤5th percentile) on one or more cognitive tests. Results of the separate cognitive tests are shown in table 5.2.

Table 5.1 Characteristics of aSAH patients (N=109).

Demographic characteristics	n	(%)
Sex (Female)	80	73.4
Mean age in years (range)	53 (21-85)	
Educational level		
Low (Verhage 1-3)	23	21.1
Middle (Verhage 4-5)	65	59.6
High (Verhage 6-7)	21	19.3
Clinical characteristics		
Time between aSAH and NPE (weeks; mean, range)	9 (3-23)	
Clinical condition on admission (PAASH)		
I = GCS 15	80	73.4
II = GCS 11-14	25	23.0
III = GCS 8-10	0	0.0
IV = GCS 4-7	1	0.9
V = GCS 3	2	1.8
Missing	1	0.9
Location of aneurysm		
Anterior cerebral, pericallosal and anterior communicating	52	47.7
Middle cerebral	15	13.8
Internal carotid (including posterior communicating)	27	24.7
Posterior circulation	14	12.8
Other	1	0.9
Aneurysm treatment		
Coiling	78	71.6
Clipping	30	27.5
Other	1	0.9

aSAH = aneurysmal Subarachnoid Hemorrhage; NPE = Neuropsychological Examination; PAASH = Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage; GCS = Glasgow Coma Scale.

Table 5.2 Results of the neuropsychological examination (N=109).

Cognitive domain	Test	Sample	Impaired test score (≤5th percentile)	
		n	n	%
Memory	Digit Span Backward	109	2	2.8
	RAVLT direct	107	40	37.4
	RAVLT delayed	107	32	29.9
	RAVLT recognition	105	16	15.2
	Rey-CFT delayed	101	16	15.8
	Category Fluency	107	5	4.7
Attention	Digit Span Forward	109	1	0.9
Executive functioning	Phonological Fluency	106	18	17.0
Visuospatial functioning	Rey-CFT copy	106	21	19.8

RAVLT = Rey Auditory Verbal Learning Task; Rey-CFT = Rey-Osterrieth Complex Figure Test.

Table 5.3 Results linear regression analyses to the relationship between ventricular volume (ml) and cognitive outcome (raw scores CLCE-24 and NPE).

	Ventricular volume			
	Total		Temporal horns	
	B	(95% CI)	B	(95% CI)
Cognitive complaints				
CLCE-24	0.008	(-0.011 - 0.028)	-	-
Cognitive functioning				
Memory				
Digit Span Backward	-0.003	(-0.012 - 0.007)	-0.016	(-0.091 - 0.060)
RAVLT direct	-0.036	(-0.116 - 0.045)	-0.369	(-0.979 - 0.241)
RAVLT delayed	-0.009	(-0.033 - 0.016)	-0.114	(-0.302 - 0.075)
RAVLT recognition	0.010	(-0.010 - 0.029)	0.060	(-0.089 - 0.210)
Rey-CFT delayed	-0.053	(-0.107 - 0.001)	-0.524	(-0.932 - -0.116)
Category Fluency	-0.039	(-0.118 - 0.039)	-0.379	(-0.994 - 0.235)
Attention				
Digit Span Forward	0.000	(-0.008 - 0.009)	-	-
Executive functioning				
Phonological Fluency	-0.003	(-0.067 - 0.061)	-	-
Visuospatial functioning				
Rey-CFT copy	-0.006	(-0.036 - 0.024)	-	-

RAVLT = Rey Auditory Verbal Learning Task; Rey-CFT = Rey-Osterrieth Complex Figure Test.

Relationship ventricular volume and cognitive outcome

Total ventricular volume was not related to the sum of all cognitive complaints (B = 0.008, 95%CI -0.011 to 0.028, *p*=0.40), but the volume of the temporal horns showed a significant relationship with the presence of memory complaints (B= 0.19, 95% CI 1.03 to 1.42, *p*=0.02). Linear regression analyses showed that total ventricular volume was not related to any of the neuropsychological tests (for results of separate tests see table 5.3). The volume of the temporal horns of the ventricles was only significant related to the Rey-CFT delayed recall score (B =-4.88, 95% CI -8.96 to -0.80, p=0.02). In addition to age (10.7%), the volume of the temporal horns explained 5.5% of the variance of Rey- CFT-delay. In figure 5.1 the volume of the temporal horns is plotted in relation to tests scores on the Rey- CFT delayed recall. As shown in this figure, on an individual level, volumes of the temporal horns are not higher in patients with impaired tests scores on the Rey- CFT delayed recall (grey area) compared to patients with non-impaired scores on the delayed recall of the Rey- CFT.

A sensitivity analysis for patients with the largest ventricular volume within two days after aSAH (n=85) showed again that the volume of the temporal horns was related to the delayed recall of the Rey- CFT B =-0.557, 95% CI-1.008 to -0.107, *p*=0.02).

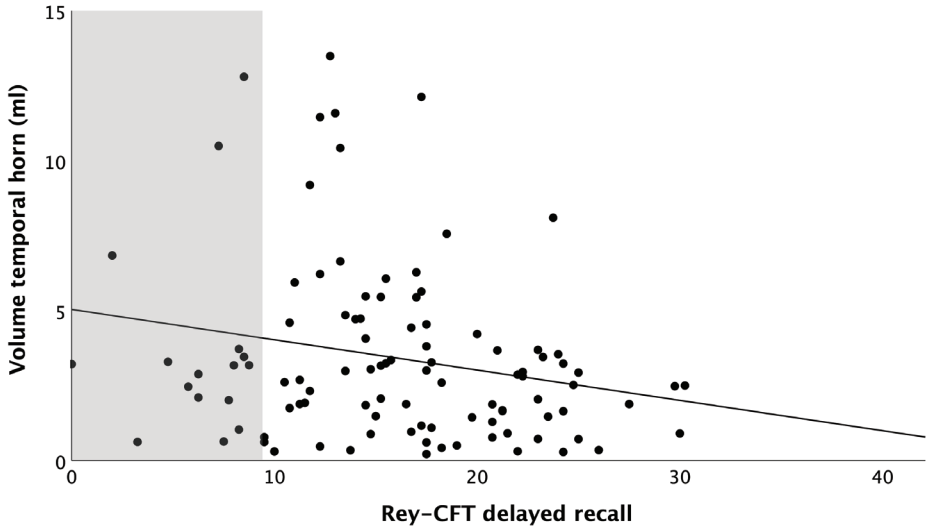

Figure 5.1 Scatterplot of the linear relationship between volume of the temporal horns (ml) and the raw score on the delayed recall of the Rey-Osterrieth Complex Figure (Rey- CFT) corrected for sex, age and level of education based on normative data.[22]

The black line is the regression line. The grey area shows the range of impaired (≤5th percentile) Rey-CFT delayed recall test scores (based on normative data).

DISCUSSION

Total ventricular volume in the (sub)acute phase after aSAH is not related to cognitive outcome (complaints and functioning) at follow up, but the volume of the temporal horns is. Patients with larger volumes of the temporal horns in the (sub)acute phase after aSAH not only report more often memory complaints, but also have lower scores on the delayed Rey- CFT, a visual memory test, performed 3 months after aSAH.

That cognitive outcome is not globally affected by ventricular size, but specifically memory is vulnerably for enlarged temporal horns, is in line with the hypothesis that the effect of ventricular volume on memory is caused by pressure of the temporal horn on the hippocampus.[10] On an individual level the volume of the temporal horns does not distinguish patients with and without memory impairments. Reasons may be that memory function is not only determined by enlarged temporal horns, but also by other factors in the (sub)acute phase after aSAH such as total amount of extravasated blood, global cerebral edema or the method of aneurysm treatment.[12,23,24]

With respect to cognitive functioning, the effect of the volume of the temporal horns is only found on one of the memory tests (Rey-CFT delayed recall) included in our study. The reason that only the delayed recall of the Rey-CFT was related to the volume of the temporal horns, might be because this is an *incidental* memory test. In this test patients are, without any forewarning, asked to draw a complex figure by heart, which they have seen and copied once before (10-30 minutes).[20] In the other tests in our NPE, patients are explicit asked to remember the information (Digit Span Backward, WAIS) or retrieve semantic information (Category Fluency). The combination of the delayed and incidental aspects, the single presentation and complexity of the information that needs to be reproduced, makes the delayed recall of the Rey-CFT a sensitive memory test that quite adequately mimics memory tasks in our daily life.

Strengths of our study are that we exclusively focused on the effect of ventricular size on cognitive outcome by excluding patients with secondary neurological complications, used accurate (volumetric) measurements to assess ventricular size and analyzed not only the effect of total ventricular volume, but also the volume of the temporal horns on cognitive outcome separately. Moreover, we not only examined the relationship between ventricular size and cognitive functioning but also took patients own (subjective) evaluation about their cognitive functioning (cognitive complaints) into account. By including only patients who were discharged home or to rehabilitation center with intention to be transferred home in 3 months, patients in our sample had a relatively good functional outcome. They are, however, the patients who experience considerable cognitive complaints and cognitive

impairments which are not well understood. Because we focused only on the volume of the ventricles in the initial two weeks after aSAH and excluded patients with secondary hydrocephalus, our findings cannot not be generalized to patients with delayed or chronic enlarged ventricles.

CONCLUSION

On group level the effect of volume of the temporal horns on memory is small but significant. Since on an individual level the volume of the temporal horns does not distinguish between patients with and without memory impairments on follow up, our study gives no indication for aggressive drainage in patients with enlarged ventricles but without symptoms in the acute phase after aSAH. Future studies are required to examine how the volume of the temporal horns develops over time and its effect on memory in the longer term.

ACKNOWLEDGEMENTS

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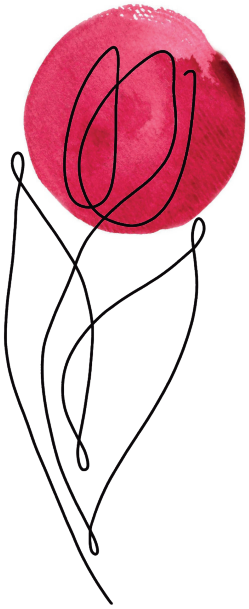
PART II

Determinants of psychosocial outcome after aSAH

CHAPTER 6

Exploratory study of the course of posttraumatic stress disorder after aneurysmal subarachnoid hemorrhage



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ABSTRACT

Introduction

Posttraumatic stress disorder (PTSD) occurs often in aneurysmal subarachnoid hemorrhage (aSAH) survivors, but how PTSD develops over time post-aSAH is still unclear. We examined the course of PTSD symptoms during the first year after aSAH.

Methods

In this prospective cohort study, the Impact of Event Scale (IES) was applied in 128 patients 3, 6 and 12 months after aSAH. Multilevel modelling was used to assess changes in levels of PTSD symptoms over time and to explore if demographic characteristics, aSAH characteristics, level of education, cognitive functioning and neuroticism are associated to the course of PTSD symptoms.

Results

Multilevel analyses showed at group level no differences in the average level of PTSD symptoms between 3, 6 or 12 months post-aSAH ($p = 0.22$). At individual level, changes in PTSD symptoms over time were present (X^2 (121) = 149.73 $p = 0.04$). None of the factors could explain the variance in change of PTSD symptoms over time.

Conclusions

The course of PTSD appears to differ between individuals after aSAH. We found no factors that explain these differences. There is not one optimal moment in time to assess PTSD. Therefore, it is important to assess PTSD at several time points after aSAH.

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) constitutes 5% of all strokes. It is characterized by an acute onset of the most severe headache ever, which can be accompanied by focal neurological deficits and depressed consciousness.[1] The (acute) clinical symptoms and postictal events of an aSAH are without doubt stress-evoking and can for some be a traumatic experience sufficient to elicit a posttraumatic stress disorder (PTSD),[2-4] even in the chronic phase after aSAH.[5,6] Most of previous studies regarding PTSD after aSAH are executed within the first year after aSAH.[3,7-9] The rates of PTSD found in these studies vary between 18% and 37% and show no clear pattern of PTSD symptoms over time.

Traditional models of PTSD (of all causes) show that there are individual differences in the course of PTSD. Some people will never develop PTSD, some will recover from initially experiencing PTSD, but there are also people who show either delayed or chronic PTSD.[10-12] PTSD due to a medical event or diagnoses may conceptually and experientially diverge from traditional models of PTSD. According to Edmondson's Enduring Somatic Threat (EST) model, PTSD due to an acute life-threatening medical event differs from PTSD due to past, discrete external traumatic events (such as combat), in the source of the threat (somatic versus external), the temporal focus of threatening cognitions (present/future versus past) and the types and consequences of avoidance behavior and hyperarousal.[13] The course of PTSD symptoms may also differ according to the different triggers for PTSD. The enduring character of the features causing PTSD symptoms after a medical event might lead to more chronicity of the PTSD symptoms. Longitudinal studies to PTSD after aSAH are scarce and only analyzed change of PTSD over time at group level.[8,9,14,15] The individual differences in the course of PTSD symptoms after aSAH are therefore still unclear.

Demographic characteristics such as sex and age, educational level and cognitive performance, the personality characteristic neuroticism and severity of the trauma are often found to be related to PTSD.[16-21] If these factors also play a role in the differences in the course of PTSD is however unknown. According to the EST model, PTSD symptoms due to a medical event are strongly associated with the ongoing consequences of the event.[13] This suggests that the persistent deficits after aSAH, such as cognitive deficits, play a central role in the maintenance of PTSD symptoms after aSAH. Moreover, neuroticism might influence the course of PTSD because the predisposition to experience negative emotions such as worry, may aggravate the experience of persisting negative consequences of the aSAH and therefore sustain PTSD symptoms.

Hence, the first aim of this study is to determine individual differences in the course of PTSD symptoms after aSAH. The second aim is to explore if factors that are often related to PTSD, can also explain differences in the course of PTSD. Studying the course of PTSD and its explanatory factors might help clinicians to timely signal PTSD symptoms after aSAH.

METHODS

Patients and procedure

This study was approved by the Medical Ethics Review Committee of the University Medical Center of Utrecht. Patients were retrieved from a prospectively collected series of patients coping with aSAH admitted to the University Medical Center of Utrecht and visited the outpatient clinic for aSAH patients for a follow up according to routine 3 months post-aSAH between March 2011 and December 2013. Study inclusion criteria were (1) SAH was caused by an aneurysm as proven by CT, MR or conventional angiography; (2) proficiency in the Dutch language, and (3) no known illness with a life expectancy < 1 year. Data on demographics and aSAH characteristics were retrieved from the prospective database of the Department of Neurology and Neurosurgery of University Medical Center of Utrecht. Prior to the visit to the outpatient clinic and at 6, and 12 months post-aSAH, all patients were asked to complete a self-report questionnaire regarding PTSD symptoms, which was sent by mail. Selfcare & mobility and cognitive functioning were assessed during the visit at the outpatient clinic (3 months post-aSAH). In addition, a questionnaire measuring the personality trait neuroticism was sent by mail at 6 months.

Posttraumatic stress symptoms

Symptoms of posttraumatic stress were assessed with the Dutch translation of the Impact of Event Scale (IES).[22] The IES is a self-report screening instrument designed to evaluate subjective distress related to a specific traumatic event. The Dutch version of the IES shows a good reliability and was validated using a factor analysis and comparisons with the Dutch version of the Dissociation Experience Scale (DES) and the Dutch version of the Symptom Checklist–90 (SCL-90).[23] The IES was administrated at the aSAH outpatient clinic, 6 months and 12 months post-aSAH to estimate the course of PTSD. Patients were asked to relate the occurrence of symptoms in the questionnaire to the aSAH as a triggering event. In case of heightened scores on the IES, patients were asked whether they were familiar with the PTSD symptoms from before the aSAH or that all symptoms were related to the aSAH. The scale contains 15 items leading to a total score ranging from 0 to 75. In this study both the total score and a dichotomized score of the IES (cut-off score $\geq$ 26)[22] were used.

Demographics and aSAH characteristics

Demographic data included sex and age. The following aSAH characteristics were retrieved from the aSAH database: (1) clinical condition on admission, (2) method of treatment of the ruptured aneurysm, and (3) neurological complications during clinical course. The clinical condition at admission was graded using the World Federation of Neurological Surgeons (WFNS) SAH grading scale.[24] A WFNS rating of I-III was classified as good clinical condition and a WFNS rating of IV-V as poor clinical condition. The received treatment for the ruptured aneurysm was divided into surgical versus endovascular. Hydrocephalus, secondary bacterial meningitis, rebleeding and secondary ischemia were noted as neurological complications and for analyses dichotomized in presence or absence of medical complications.

Selfcare & mobility, level of education, cognitive functioning and neuroticism

Selfcare & mobility were assessed by a nurse practitioner using the 10-item version of the Barthel Index (score range 0–20).[25] Level of education was ranked on a 7-point scale from 1 (did not finish primary school) to 7 (university degree) and dichotomized as low-average (0–5) and high (6–7).[26] The presence of cognitive impairment(s) was examined by a neuropsychologist, using a neuropsychological examination covering six cognitive domains (see Table 6.1). Raw scores from individual tests were converted to *z*-scores based on the means and standard deviations of the sample. Subsequently, the *z*-scores belonging to the same cognitive domain were averaged to create domain scores. A total score of cognitive functioning was derived by the average of all the domain scores and used for analyses. The personality trait neuroticism was measured using the total score on the Dutch version of the neuroticism subscale of the Eysenck Personality Questionnaire Revised-Short Form (EPQR-S) (range 0–12).[27,28]

Analyses

For the statistical analyses SPSS (version 20) and HLM (version 7) software for Windows were used. To describe and visualize the course of PTSD at group level, the dichotomized IES score (cut off score ≥ 26) was used. For this description and visualization, only patients coping with aSAH, of whom all three IES assessments were available could be included. Analyzing differences in the course of PTSD symptoms at individual level and its explanatory factors, requires multilevel modelling. This analysis uses a continuous score (total score of the IES) and is able to control for missing data. In case items on the IES scale were missing, items were inferred using person-mean substitution if no more than three items (≤20%) were missing. When one or two of the three IES scales of a patient was missing completely (not sent back), data was inferred by multilevel-analyses (likelihood-based estimation).[29] Prior to the analysis, all scale variables were tested for normality and transformed using square root transformations if positively skewed. In

our design, measurements in time are nested within individuals, resulting in a two-level hierarchy existing of occasion-level (T1, T2 or T3) (level 1; within subjects) and subject-level (level 2; between subjects). In this dataset, time is the only independent variable at the occasion-level. Sex, age, educational level, clinical condition on admission score, treatment aneurysm, neurological complications, cognitive functioning and the personality trait neuroticism represent between-person differences and are independent variables at the subject-level. First, we checked if the level of PTSD changes over time (differences between average T1, T2 & T3) on group level. In order to assess differences in the course of PTSD on an individual level, we tested whether the variance around the regression slope was significant. Subsequently, we explored which factors can explain differences in the average level of PTSD between individuals by adding the independent level-2 variables. To preserve enough power in the analyses the independent variables were added in clusters. First demographic variables (age and sex) were included. In the next models, one by one the clusters 'aSAH characteristics' (WFNS, complications and treatment), 'level of education & cognitive functioning' and 'neuroticism' were added alternately to the model. When testing each cluster of person-variables, exploratory interactions between time and the relevant person-variables were conducted to identify what factors can explain individual differences in change of the level of PTSD over time. Statistical significance was determined with a *p*-value of $\alpha = 0.05$.

RESULTS

aSAH population

During the study period, 172 patients met the inclusion criteria. For 3 patients, the IES-scale was missing at all assessments. The neuropsychological examination was not administrated for 8 patients, of whom 7 had completed a neuropsychological test battery elsewhere recently and 1 patient was diagnosed with pre-existent intellectual disability. For another 7 patients, cognitive data were incomplete (for > 4 of the 5 cognitive domains), because of lack of time, fatigue or visual problems. The EPQR-S was not sent back by 27 patients. Of the remaining 128 patients, 94 completed the IES at all three assessments, 28 at two measurements and 6 patients at only one measurement. All 128 patients were included in the multilevel analyses. At group level, patients with a complete dataset did not differ significantly from the patients with incomplete data in terms of demographics, aSAH characteristics, cognitive functioning or neuroticism (all $p > 0.1$). Table 6.2 shows the demographics and aSAH characteristics of the study population. At the time of their visit to the outpatient clinic, 102 patients (80%) were living at home, 19 (15%) stayed at a rehabilitation center, and 7 (5%) were living at a nursing home.

Table 6.1 Tests included in the cognitive screening at the outpatient aSAH clinic.

Cognitive domain		Neuropsychological test
Language		
	Word-finding	Boston Naming Task (shortened version)
Memory		
	Working memory	WAIS-III Backward Digit Span
	Verbal memory	Rey Auditory Verbal Learning Task (RAVLT)
	Non-verbal incidental memory	Delayed Rey-Osterrieth Complex Figure Test (Rey-CFT)
	Semantic memory	Category Fluency (animals)
Attention		
	Attention span	WAIS-III Forward Digit Span
	Switching	TEA Visual elevator (shortened version)
Executive functions		
	Concept generation	Phonological Fluency ('N' and 'A')
	Planning	BADS Key Search
	Inhibition	FAB Go-No go
Processing speed		
		WAIS-III Digit Symbol Coding
Visuospatial functions		
	Visual perception	Judgement of Line Orientation (JULO)
	Visuoconstruction	Copy score of the Rey-CFT

WAIS-III: Wechsler Adult Intelligence Scale III; BADS: Behavioral Assessment of the Dysexecutive Syndrome; TEA: Test of Everyday Attention; FAB: Frontal Assessment Battery.

Course of PTSD symptoms

Group level

In the multilevel analyses the effect of Time on the IES score was not significant ($p = 0.218$), meaning that the average level of PTSD symptoms at group level did not change over time.

Individual level

Figure 6.1 gives an overview of the different courses of PTSD present in the sample, based on a dichotomous measure of PTSD. In this figure, only patients with all three assessments available are included (n = 94). The figure shows that most patients (56.4%) had no symptoms or did not reach the cut-off score for PTSD in the first year post-aSAH. At the initial assessment (3 months) 14.9% had scores suggestive of PTSD, but showed recovery later on, 8.5% had symptoms indicative of PTSD at all three measurements, and 12.8% of the patients showed delayed PTSD.

The multilevel analysis used the continuous measure of PTSD and because its ability to control for missing data all 128 patients coping with aSAH could be included. The analysis showed a significant variance around the regression slope ($\chi 2$ (121) = 149.73 p = 0.039) of the Time variable. This means that the regression coefficient of the Time variable differs between individuals and confirms that the individual differences in the course of PTSD are significant.

Table 6.2 Sample characteristics (n=128).

	n	%
Demographics		
Sex (female)	85	66.4
Mean age in years (SD)	56 (12.6)	
Education level		
Low-average	100	78.1
High	28	21.9
aSAH characteristics		
Clinical condition on admission		
Good (WFNS I-III)	105	82.0
Poor (WFNS, IV-V)	23	18.0
Aneurysm location		
Anterior circulation	109	85.2
Posterior circulation	19	14.8
Aneurysm treatment		
Surgical	47	36.7
Endovascular	81	66.3
Complications (yes %)		
Rebleeding	8	6.3
Secondary ischemia	17	13.3
Hydrocephalus	13	10.2
Sec. bact. meningitis	1	0.8
>1 complication	12	9.4
Clinical characteristics		
Mean follow up time after aSAH in weeks (SD)	9.5 (3.0)	
Selfcare and mobility		
Complete independence (BI 20)	115	89.8
Nearly independence (BI 15-19)	5	3.9
Assisted dependence (BI 10-14)	8	6.3

aSAH = aneurysmal Subarachnoid Hemorrhage; WFNS = World Federation of Neurological Surgeons; BI = Barthel Index.

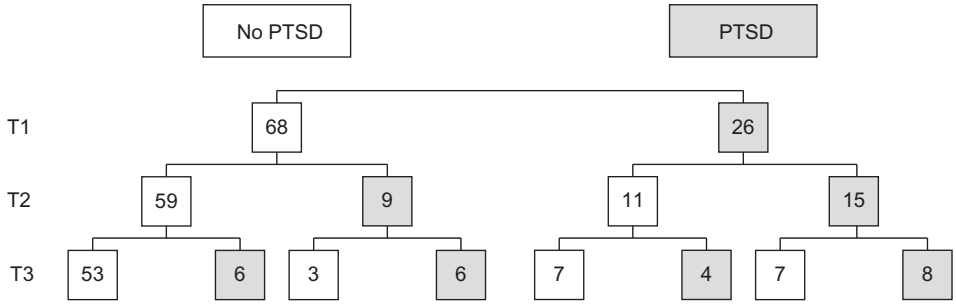

Figure 6.1 Course of PTSD based on the frequency of patients with symptoms (not) suggestive of PTSD at 3 months (T1), 6 months (T2) and 12 months (T3) after aSAH (n=94).

Explaining variance in PTSD

When entering the person-variables to the multilevel model in clusters, only neuroticism was (positively) significantly related to the average level of PTSD $t(124) = 7.245, p < 0.001$.

There were no significant interactions between the Time variable and each of the person-variables (sex, age, neurological complications, treatment aneurysm, level of education, cognitive functioning, neuroticism), which means that none of the person-variables could explain the differences in the change of PTSD over time (variance of the regression slope) between individuals. Regression coefficients and standard errors of each model of the multilevel regression analysis are displayed in the Supplementary File S6.1.

DISCUSSION

There is substantial heterogeneity in the course of PTSD symptoms in the first year post-aSAH. About half of the patients do not experience symptoms indicative of PTSD, 15% of all patients show recovery after symptoms indicative of PTSD at the initial assessment, 9% experience symptoms indicative of PTSD at all assessments and 13% show delayed symptoms indicative of PTSD.

Previous aSAH studies on PTSD have described a stable course or a pattern of recovery of PTSD.[8,9,14,15] However, 'delayed PTSD' in which patients initially do not experience PTSD but develop PTSD in a later stage after aSAH has not been described yet. The reason for this new finding is that contrary to all previous longitudinal studies on PTSD after aSAH, we have not only analyzed changes of PTSD symptoms over time at group level but also analyzed at an individual level.

That the majority of the patients do not experience PTSD symptoms during the first year after aSAH is in line with findings of previous studies to the course of PTSD after a traumatic event (of all causes).[11] We did not test whether PTSD was related to the frequency of headaches after aSAH, heart rate, or other physiological sensations that may be interpreted as impending aSAH or actual aSAH recurrence, as predicted by the EST model. However, cognitive deficits were unrelated to PTSD symptoms. None of the clinical outcome factors were related to the course of PTSD after aSAH.

Although the study provides new insights into the course of PTSD symptoms after aSAH, there are limitations which deserve mentioning. We used a self-report questionnaire to screen for PTSD symptoms, which can lead to an overestimation of PTSD compared to diagnosis of PTSD by a formal psychiatric interview.[7] The amount of patients coping with aSAH who report symptoms suggestive of PTSD in our study does however not deviate from previous studies into PTSD in the first year after aSAH.[3,7-9] Another limitation is that the multilevel analysis used in this study, expresses the course of PTSD symptoms in one continuous score (regression slope) and cannot address categorical trajectories typically described after PTSD.[12] Factors explaining differences in the course of PTSD (variance around the regression slope), therefore cannot be related to separate trajectories. Advanced data analytic methods, such as latent growth mixture modelling, are developed to identify and predict data driven trajectories and might therefore be more optimal to analyze longitudinal PTSD data. These techniques require however a substantially larger sample size, which with the prevalence of aSAH will be difficult to achieve. Lastly, we did not include data about the treatment patients received during the follow up period regarding the PTSD symptoms. The effectiveness of treatment of PTSD depends not only on the type of intervention, but also on other factors such as sex and age of the patient, duration of PTSD before treatment, and co-morbidity.[30-31] This complexity makes it difficult to control for treatment in longitudinal studies on PTSD.

Because half of the patients who experience symptoms suggestive of PTSD one year after aSAH do not experience these symptoms at initial assessment (3 months), it is important to assess PTSD symptoms at various points in the initial year post-aSAH. Not only because patients with delayed onset of PTSD might otherwise be missed by professionals, but also because 70% of people with PTSD symptoms do not seek professional help for their condition. This despite the negative effects of PTSD on daily life and the availability of treatment.[31] Further research is needed to better understand which patients experience chronic PTSD after aSAH and which patients develop delayed PTSD. Since none of the factors included in this study were associated with the course of PTSD, other factors such as passive coping style, psychiatric history, fears of recurrence and illness perceptions[2,6,7,9,32] or the level of social support and additional life stress[33] should be considered to explain the differences in variation of PTSD over time.

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SUPPLEMENTARY FILES

S6.1 Results statistical analyses of the course of PTSD symptoms on individual level

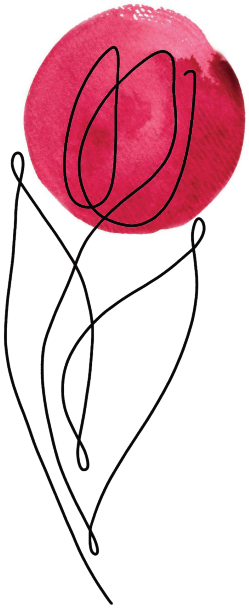
Supplement 6.1 Results multilevel analyses (n=128)

Model:	M_2: time random	M_3: + demographic variables	M_4: + aSAH characteristics	M_5: + education and cognition	M_6: + neuroticism
Fixed part	coeff. (s.e.)	coeff. (s.e.)	coeff. (s.e.)	coeff. (s.e.)	coeff. (s.e.)
Intercept	3.47 (0.20)***	3.12 (0.35)***	3.45 (0.40)***	3.23 (0.34)***	3.35 (0.25)***
Time	-0.11 (0.10)	0.01 (0.18)	-0.20 (0.16)	-0.08 (0.12)	-0.10 (0.10)
Sex		0.54 (0.42)	0.35 (0.38)	0.34 (0.37)	0.15 (0.29)
Age		-0.01 (0.02)	-0.01 (0.01)	-0.01 (0.01)	0.01 (0.01)
Time*Sex		-0.19 (0.21)			
Time*Age		0.01 (0.01)			
WFNS			0.12 (0.54)		
Complications			-0.24 (0.46)		
Treatment			-0.40 (0.42)		
Time*WFNS			0.04 (0.26)		
Time*Complications			0.14 (0.22)		
Time*Treatment			0.07 (0.21)		
Education				0.06 (0.54)	
Cognition				-0.28 (0.37)	
Time*Education				-0.13 (0.27)	
Time*Cognition				-0.13 (0.18)	
Neuroticism					0.34 (0.05)***
Time* Neuroticism					0.02 (0.03)
Random part	Variance (s.d.)	Variance (s.d.)	Variance (s.d.)	Variance (s.d.)	Variance (s.d.)
r_0	3.51 (1.87)***	3.45 (1.86)***	3.41 (1.85)***	3.42 (0.85)***	2.04 (1.43)***
r_1	0.27 (0.52)*	0.25 (0.50)*	0.26 (0.51)*	0.26 (0.51)*	0.29 (0.54)*
e	1.60 (1.26)	1.60 (1.27)	1.60 (1.26)	1.59 (1.26)	1.56 (1.25)
Deviance	1406.87	1404.59	1404.45	1402.57	1336.89
Number of estimated parameters	6	10	14	12	10

* $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.

CHAPTER 7

Restrictions and satisfaction with participation in patients who are ADL-independent after an aneurysmal subarachnoid hemorrhage



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ABSTRACT

Introduction

Most survivors of an aneurysmal subarachnoid hemorrhage (aSAH) are ADL-independent, but they often experience restrictions in (social) activities and, therefore, cannot regain their pre-morbid level of participation. In this study, participation restrictions and participation satisfaction experienced after aSAH were assessed. Moreover, possible predictors of participation after aSAH were examined to identify goals for rehabilitation.

Methods

Participation restrictions experienced by a series of 67 patients visiting our SAH outpatient clinic were assessed as part of standard clinical care using the Participation Restrictions and Satisfaction sections of the Utrecht Scale for Evaluation of Rehabilitation Participation (USER-Participation) 6 months after aSAH. Cognitive impairments, cognitive and emotional complaints, and symptoms of depression and anxiety, assessed 10 weeks after aSAH, were examined as possible predictors of participation by means of linear regression analysis.

Results

Although patients were ADL-independent, 64% reported one or more participation restrictions and 60% were dissatisfied in one or more participation domains. Most commonly experienced restrictions concerned housekeeping, chores in and around the house, and physical exercise. Dissatisfaction was most often reported about outdoor activities, mobility, and work/housekeeping. The main predictors of participation restrictions as well as satisfaction with participation were cognitive complaints (subjective) ($B = -0.30$, $p = 0.03$ and $B = -0.40$, $p = 0.002$, respectively) and anxiety ($B = 0.32$, $p = 0.02$ and $B = -0.34$, $p = 0.007$, respectively).

Conclusions

Almost two-thirds of the ADL-independent patients experienced problems of participation 6 months after aSAH. Cognitive complaints (subjective) and anxiety symptoms showed the strongest association with participation restrictions and satisfaction. Cognitive rehabilitation and anxiety-reducing interventions may help to optimize rehabilitation and increase participation after aSAH.

INTRODUCTION

Two-thirds of patients with an aneurysmal subarachnoid hemorrhage (aSAH) survive.[1] Although most of these patients regain independence in basic activities of daily living (ADL), many nevertheless report restrictions in resuming more complex activities such as housekeeping, work, and social relationships.[2] These complex activities can be described as 'participation', which is defined in the International Classification of Functioning, Disability and Health (ICF) as 'the involvement of an individual in a life situation' and represents the social perspective on functioning.[3] It is especially because aSAH patients are relatively young that restrictions in participation can have a major impact on their lives.

Clinical rehabilitation aims to minimize the consequences of aSAH with the ultimate goal of restoring participation. ADL-independent patients are usually not referred to outpatient therapy programs. Being ADL-independent does however not mean that someone is able to resume his or her previous level of social functioning and can return to the premorbid role in community. The level of participation in these patients might therefore not completely be regained.

Some studies have described elements of participation after SAH, especially the ability to return to work.[4-6] These studies have led to an extension of knowledge about the impact and determinants of reintegration into work. However, other aspects of participation, such as leisure or contact with family or friends, have received less attention. When a patient is able to return to work, these other complex activities and someone's social role fulfillment might still be hampered and of great importance to the patient and his or her environment. As far as we are aware, there are no studies in aSAH patients which studied all aspects of participation. This study will therefore obtain an overview of the level of the different aspects of participation after aSAH.

The second aim of this study was to identify what factors are associated with participation after aSAH. Cognitive impairments (objective), cognitive complaints (subjective), and psychological factors such as mood and anxiety have often been related to adverse functional outcome after aSAH.[2,7-10] In a previous study on participation after ischemic stroke, better participation was associated with both higher (cognitive) independence as well as less mood problems.[11] Based on these findings, this study will determine the associations between cognitive and psychological factors and participation among ADL-independent aSAH patients. Insights into the associations can help clinicians decide what aspects to focus on in rehabilitation to improve participation after aSAH.

METHODS

The study was approved by the University Medical Center Utrecht (UMCU) Medical Ethics Committee. Data were derived from a prospective data collection according to clinical care as usual; therefore, no informed consent was used.

aSAH patients and procedure

In this consecutive case series, patients with an SAH caused by an aneurysm as proven by CT, MR, or conventional angiography were included. According to standard clinical care at the UMCU, these patients are invited to visit the SAH outpatient clinic 10 weeks after discharge. Less than a week before visiting the outpatient clinic, patients are asked to fill in the Hospital Anxiety and Depression Scale (HADS), which is sent by mail, and take the completed questionnaire to their appointment at the SAH outpatient clinic. At this clinic, patients are first seen by a nurse-practitioner specialized in SAH who administers the Checklist for Cognitive and Emotional consequences following stroke (CLCE-24). After this, patients are seen by a neuropsychologist for a brief cognitive assessment, which includes a cognitive screening instrument, consisting 18 items measuring orientation, memory function, language, attention, executive functioning, and visuospatial functioning (for details, see Supplementary file S4.1.2 of Chapter 4). Finally, a rehabilitation physician performs a physical examination and evaluates the need for additional therapy based on the presence of physical, cognitive, or emotional deficits or complaints and already provided care. Six months after the aSAH, patients are invited by mail to complete and return the Restrictions and Satisfaction sections of the Utrecht Scale for Evaluation of Rehabilitation Participation (USER-Participation), which measures the level of restrictions and satisfaction of patients' participation. For this study, data are used from patients who had visited the outpatient clinic between February 2010 and February 2011 and were functionally independent. Functionally independence was measured with the 10-item version of the Barthel Index. Only patients with a maximal score (Barthel score: 20/20) were included in the study. Patients who had not completed the brief cognitive assessment or questionnaires (CLCE-24, HADS, USER-Participation) were excluded from the analyses.

Participation (6 months after aSAH)

Six months after the aSAH participation was assessed by means of the Restrictions subscale and the Satisfaction subscale of the USER-Participation instrument.[11-13] This instrument specifically aims at participation and is validated in a previous study using the Frenchay Activities Index (FAI), the Participations subtotal score of the ICF Measure of Participation and Activities Screener (IMPACT-SP) and the Participation Scale as reference measures.[12] The FAI, IMPACT-SP, and Participation Scale measure functional status or participation

and can be used to monitor recovery during rehabilitation. The FAI records the frequency of instrumental activities of daily living (IADL) performed by the patient in the last 3–6 months by scoring 15 activities on a scale from 0 (never) to 3 (high frequency, which is per activity described in more detail).[14] The IMPACT-SP measures experienced limitations in participation in 15 items, which need to be scored on a 4-point scale ranging from 0 (no, no limitations whatsoever) to 3 (yes, I cannot do that at all).[15] The Participation Scale is a self-report instrument to assess the level of participation compared to peers on 18 items. In case of a lower level of participation, the extent to which the respondent experiences this as a problem can be described in a 4-point scale ranging from score 1 (no problem) to score 5 (large problem).[16] The USER-Participation, which was used to measure participation in this study, has strong correlations with the FAI, IMPACT-SP, and the Participation Scale. Moreover, the USER-Participation shows good reproducibility.[13] The Restrictions subscale of the USER-Participation instrument consists of 10 items and concerns activities of daily life such as work, household, leisure, and visiting others. The score on each item ranges from 0 (not possible) to 3 (without difficulty). The Satisfaction subscale contains 9 items relating to satisfaction with various aspects of participation, e.g., self-care, leisure, work, and social relationships. Each item score ranges from 0 (very dissatisfied) to 4 (very satisfied). The sum scores of the Restrictions and Satisfaction subscales are both converted to a 0–100 scale. Higher scores indicate good levels of participation (less restrictions, greater satisfaction). The prevalence of restrictions and dissatisfaction is expressed by dichotomizing these scores based on the presence (1) or absence (0) of a restriction or dissatisfaction regarding the activity.

Possible predictors of participation

Demographic data and aSAH characteristics were obtained from the collected database of the Department of Neurology and Neurosurgery of the UMCU. Level of education was measured by a Dutch classification system ranging from 1 (did not complete primary school) to 7 (university degree) and dichotomized as low (0–5) and high education (6–7).[17]

The aSAH characteristics include clinical condition on admission, the location of the aneurysm, the method used to occlude the aneurysm and complications after the aSAH. The clinical condition on admission was measured with the World Federation of Neurosurgical Societies (WFNS) SAH grading scale, which is a SAH grading scale based on the Glasgow Coma Scale (GOS) and additionally differentiates in the presence or absence of focal neurological deficits for GCS scores 13 and 14.[18] For this study, the WFNS scores were dichotomized into good (I–III, GCS 13–15) and poor (IV–V, GCS 3–12) clinical condition on admission. Location of the aneurysm was categorized into anterior and posterior circulation.

Cognitive and emotional complaints were assessed by administering the Checklist for Cognitive and Emotional consequences following stroke (CLCE-24).[19] This is a valid instrument that consists of 13 items for cognitive complaints and 9 items for emotional complaints. Scores on each item were dichotomized into 0 (no complaints) and 1 (complaints).

The presence of cognitive impairments was assessed by means of a brief cognitive assessment using 18 items to screen the main cognitive domains (see Supplementary file S4.1.2 of Chapter 4). All items of this instrument are based on the concepts of standard neuropsychological tasks. First, orientation in time, place, and person is checked. Memory functions are measured by direct and delayed reproduction of five words and the location of five coins in place. Also patients are asked what they had for dinner yesterday. Language is examined by spontaneous speech, writing their name, reading a sentence, story comprehension, and naming objects and colors. Attention is assessed by means of the verbal trail making task and by patients to name the months of the year backwards. The letter-fluency ('A'), meander-task, and a maze measure executive functioning and items for visuospatial functioning include clock- and cube drawing. Each item is scored on a 3-point scale in which 0 = unimpaired representing an adequate response, 1 = mildly impaired representing a partly correct response and 2 = severely impaired in case of an incorrect or missing response. Overall cognitive functioning is measured using a sum score of all 18 items ranging from 0 (no cognitive impairments) to 36 (severe cognitive impairments).

Anxiety and depressive symptoms were assessed with the Dutch version of the Hospital Anxiety and Depression Scale (HADS)[20] which shows a good validity and reliability.[21,22] This screening instrument contains 7 symptoms for anxiety and 7 symptoms for depression. The maximum score for each subscale is 21. The cut-off score was set at 11 for both the Anxiety and Depression subscales, as this value reflects symptomatology indicative of clinical depression or anxiety disorders.[23]

Statistical analyses

For each of the two outcome measures (Participation Restrictions and Satisfaction with participation), univariable regression analyses were performed to identify potential predictors with respect to demographics (sex, age, and education), aSAH characteristics (WFNS, location of the aneurysm, presence of medical complications, and treatment of aneurysm), cognitive variables (cognitive functioning and cognitive complaints) and emotional variables (emotional complaints, symptoms of depression, and symptoms of anxiety). From the results of the univariable analyses, possible predictors with a p-value ≤ 0.1 were selected and entered into a one-block forward linear regression analysis. All predictors were checked for collinearity. In these linear regression analyses, we considered $p < 0.05$ to represent statistical significance. A sensitivity analysis was performed to control for potential bias due to missing data.

RESULTS

aSAH sample

Of the 87 patients with an aSAH who visited the outpatient clinic, 20 (23%) were not included in this study because of a Barthel Index score <20 (n = 4), missing CLCE-24 scores (n = 3) or HADS scores (n = 5), incomplete neuropsychological examination due to (severe) aphasia (n = 1), severe fatigue (n = 1), or missing or incomplete USER-Participation scores (n = 6) six months after aSAH. These patients did not differ from the included group with respect to age, sex, education, and WFNS score (all $p > 0.05$). At the time of their visit to the outpatient clinic, 56 (84%) of the 67 included patients were living at home, 9 (13%) were in a rehabilitation center and 2 (3%) were living in a nursing home. Table 7.1 lists the characteristics of the included patients.

Cognitive and emotional complaints

Fifty-four patients (81%) reported at least one cognitive complaint (subjective). Most frequently reported cognitive complaints were mental slowness (69%), problems remembering new information (42%), taking initiative (40%), and attention problems (40%). One or more emotional complaints were expressed by 64 patients (96%). Most of the emotional complaints concerned fatigue (93%), anxiety (39%), irritability (37%), and/or depression (33%).

Cognitive functioning

Fifty-four patients (81%) had a mild impairment, and more than half of the patients (57%) were severely impaired regarding at least one item on the brief neuropsychological assessment. Within the memory domain, 24% of the patients were mildly and 8% severely impaired in encoding five words. The delayed recall of these words was mildly impaired in 34% of the patients and severely impaired in 36%. Items tapping executive functioning showed mild or severe impairments in 8% of the patients. Other cognitive domains in which impairments were found included attention and visuospatial functioning. The orientation and language domains were unaffected in most of the patients.

Anxiety and depression

Nine patients (13%) had a HADS score suggestive of depression, whereas 14 patients (21%) had a score suggestive of an anxiety disorder.

Table 7.1 Characteristics of aSAH patients (n=67).

	n		%
Demographic characteristics			
Women	45		67.2
Mean age in years (SD)		53.2 (11.2)	
Education level			
Low	46		68.7
High	21		31.3
aSAH characteristics			
Mean follow-up time after aSAH in weeks (SD)		10.0 (3.1)	
WFNS SAH grading scale on admission			
I-III, GCS 13-15	61		91.0
IV-V, GCS 3-12	6		9.0
Aneurysm location			
Anterior circulation	33		49.3
Posterior circulation	34		50.7
Treatment received			
Coiling	36		53.7
Clipping	30		44.8
None*	1		1.5
Complications (yes %)			
Rebleeding	2		3.0
Secondary ischemia	5		7.5
Hydrocephalus	9		13.4
Hydrocephalus and rebleeding	1		1.5
Hydrocephalus and ischemia	1		1.5
	M	SD	
Outcome Measures			
CLCE-24			
Cognitive complaints [0-13]	2.9	2.3	
Emotional complaints [0-9]	2.8	1.8	
Neuropsychological Assessment			
Cognitive impairments [0-36]	4.6	4.2	
HADS			
Anxiety [0-21], (% score ≥ 11)	5.6	4.9	(20.9)
Depression [0-21], (% score ≥ 11)	4.6	4.3	(13.4)

aSAH = Aneurysmal Subarachnoid hemorrhage; WFNS = World Federation of Neurosurgeons; GCS = Glasgow Coma Score; HADS = Hospital Anxiety and Depression Scale.

*For a basilar top aneurysm including both posterior cerebral arteries in a patient with bilateral occluded carotid arteries.

Restrictions and dissatisfaction with participation 6 months after aSAH

The mean Restrictions score on the USER-Participation instrument was 83.7 (SD 17.5). Forty-three patients (64%) reported one or more participation restrictions. The mean Satisfaction score was 77.9 (SD 16.7). Forty patients (60%) were dissatisfied with one or more domains of participation. The most commonly experienced restrictions concerned housekeeping, chores in and around the house, and physical exercise. Dissatisfaction with participation was also reported regarding housekeeping. Other most reported activities, which were experienced as dissatisfying at the level of participation, concerned outdoor activities and mobility (Table 7.2). A sensitivity analysis showed minimal bias as a consequence of excluding patients due to incomplete forms.

Table 7.2 Participation restrictions and dissatisfaction with participation 6 months after aSAH as assessed with the USER-Participation instrument (n=67).

	n	%		n	%
Restrictions			*Dissatisfaction*		
Housekeeping	28	41.8	Outdoor activities	23	34.3
Chores in/around house	26	38.8	Mobility	20	29.6
Physical exercise	25	37.3	Work/housekeeping	20	29.6
Outdoor activities	24	35.8	Cognition	19	28.4
Work/education	21	31.3	Leisure indoors	15	22.4
Going out	20	29.9	Contact with friends	7	10.4
Visits to family or friends	18	26.9	Partner relationship	7	10.4
Leisure indoors	13	19.4	Family relationships	4	6.0
Visits from family or friends	12	17.9	Self-care	3	4.5
Telephone/computer contact	10	14.9			

aSAH = Aneurysmal Subarachnoid Hemorrhage; USER = Utrecht Scale for Evaluation of Rehabilitation
- Restrictions (not possible, with assistance or with difficulty)
- Dissatisfaction (very dissatisfied, dissatisfied or neutral)

Predictors of participation restrictions

Univariable and multivariable associations between potential predictors and participation restrictions after 6 months are shown in Table 7.3. Cognitive complaints (subjective) ($p < 0.001$), emotional complaints ($p = 0.003$), depression ($p < 0.001$), and anxiety ($p < 0.001$) were significantly associated with participation restrictions. No relationship was found between demographic, aSAH characteristics, and the objective measure of cognitive functioning and participation restrictions. The multiple regression analysis yielded two models. In model I, anxiety explained 25.4% of the variance. In model II, cognitive complaints (subjective) added 5.5% to the outcome of model I, increasing the total explained variance to 30.9%.

Predictors of satisfaction with participation

Table 7.4 shows the univariable and multivariable associations between possible predictors of satisfaction with participation 6 months after aSAH. Besides cognitive complaints (subjective) ($p < 0.001$), all psychological measurements, e.g., emotional complaints ($p < 0.001$), depression ($p = 0.003$), and anxiety ($p < 0.001$), were significantly related to satisfaction with participation, whereas demographic, aSAH characteristics, and the objective measure of cognitive functioning were not associated with satisfaction. The multiple regression analysis rendered two significant models, in which cognitive complaints (subjective) showed the largest effect (36.1%) and anxiety increased the fit of the model by 7.0% to a total explained variance of 43.1%.

Table 7.3 Predictors of Participation Restrictions 6 months after aSAH (n=67).

	Univariable Analyses		Multivariable Analysis, B (*p*-value)	
	B	*p*-value	Model I	Model II
Demographic characteristics				
Age	0.04	0.77		
Sex (female)	-0.13	0.29		
Education (high)	-0.01	0.95		
aSAH characteristics				
WFNS (high)	0.12	0.32		
Location of aneurysm (anterior)	0.20	0.11		
Complications (yes)	-0.10	0.41		
Treatment (clipping)	-0.09	0.47		
Cognitive and Psychological variables				
Cognitive functioning	-0.17	0.16		
Cognitive complaints	-0.49	< 0.001 *	-	-0.30 (0.028)
Emotional complaints	-0.36	0.003 *	-	-
Depression (yes)	-0.43	< 0.001 *	-	-
Anxiety (yes)	-0.50	< 0.001 *	0.50 (<0.001)	-0.32 (0.017)
Explained Variance (R^2)			0.254	0.309
R^2 Change				0.055

aSAH = Aneurysmal Subarachnoid Hemorrhage.

* Variables with $p \leq 0.1$ were entered in multiple analyses

Table 7.4 Predictors of dissatisfaction with participation 6 months after aSAH (n=67).

	Univariable Analyses		Multivariable Analysis, B (*p*-value)	
	B	*p*-value	Model I	Model II
Demographic characteristics				
Age	0.007	0.96		
Sex (female)	-0.09	0.46		
Education (high)	-0.12	0.34		
aSAH characteristics				
WFNS (high)	0.05	0.69		
Location of aneurysm (anterior)	0.08	0.54		
Complications (yes)	-0.02	0.91		
Treatment (clipping)	-0.06	0.62		
Cognitive and Psychological variables				
Cognitive functioning	-0.12	0.39	-	-
Cognitive complaints	-0.60	< 0.001 *	-0.60 (< 0.001)	-0.40 (0.002)
Emotional complaints	-0.47	< 0.001 *	-	-
Depression (yes)	-0.35	0.003 *	-	-
Anxiety (yes)	-0.58	< 0.001 *		-0.34 (0.007)
Explained Variance (R^2)			0.361	0.431
R^2 Change				0.070

aSAH = Aneurysmal Subarachnoid Hemorrhage.

* Variables with $p \leq 0.1$ were entered in multiple analyses.

DISCUSSION

Two of every three aSAH patients who were ADL-independent 6 months after aSAH experienced restrictions in participation, and a similar proportion were dissatisfied with their level of participation. Most commonly experienced restrictions concerned housekeeping, chores in and around the house, and physical exercise. Dissatisfaction was most often reported about outdoor activities, mobility, and work/housekeeping. This confirms previous findings about the problems aSAH patients experience with social and complex activities.[2] The participation restrictions and the level of dissatisfaction with the participation in our study overlap to a large extent, but not completely. For example,

although patients often reported restrictions regarding visits from or to friends and family, they were nevertheless usually satisfied with these relationships. This example shows that measuring both restrictions and satisfaction offers better insights into the impact of participation restrictions.

Symptoms of anxiety and cognitive complaints (subjective) appeared to be associated with restrictions of and dissatisfaction with participation after aSAH. In this study, one-fifth of the patients reported severe levels of anxiety. Both the prevalence of anxiety symptoms and the relation of these symptoms with reduced levels of participation are in line with previous findings.[24] In contrast to cognitive complaints, cognitive impairments did not appear to be associated with participation. This finding suggests that besides emotional state of a patient, participation after aSAH is for a considerable part dependent on the experience of a patient's level of functioning rather than the objective level of functioning. It should however be noted that both cognitive complaints and participation are subjective measures, which in general show weaker associations with objective measurements of these concepts.[10,12,25,26] Furthermore, although we used a comprehensive cognitive assessment to detect cognitive impairments, more subtle impairments that still could hamper participation cannot be ruled out completely.

Although this study gives a good first overview of the level of participation after aSAH, limitations of the study deserve mentioning. Most importantly, the generalizability of our results is limited because we deliberately chose to include only ADL-independent patients. This group represents the majority of all aSAH survivors who are nevertheless often not taken care of by health professionals. These patients, therefore, do not reach an optimal level of functioning, which is a missed opportunity. To improve participation in ADL-independent patients, a better understanding of factors associated with restricted levels of participation is needed. Secondly, no previous studies are found on participation in aSAH patients to contrast our results with. The level of participation restrictions described in patients one year after stroke, of whom more than three-fourths was functionally independent, was similar to our findings.[13] In a more broader context, our aSAH patients reported higher levels of participation than those described for patients with a spinal cord injury,[27] patients during inpatient rehabilitation recovering from acquired brain injury (stroke, TBI, tumor, post anoxic brain damage, neuroinflammatory disease)[28], and rehabilitation outpatients (several medical conditions such as musculoskeletal, brain injury, heart condition, chronic pain).[12] This is most likely due to the fact that the patients in these three studies were more physical dependent as compared to our patients. A third limitation of our study is the sample size. Although the sample can be considered substantial as compared to the literature,[6-11] it is still small. Results should, therefore, be interpreted with caution.

The predictors of participation after aSAH found in our study explained a total of almost one-third of the variance of the restrictions experienced and almost half of the variance of dissatisfaction with participation. Although a portion of the variance remains unexplained, the explained variance found in this study is substantial and higher than reached in, for instance, quality-of-life research.[29]

CONCLUSIONS

Measuring participation gives insight in the consequences of aSAH and thereby reveals concrete goals for rehabilitation. It provides guidance on what problems in complex and social activities to focus on. In addition, since cognitive complaints (subjective) and anxiety symptoms are risk factors for a decreased level of participation, cognitive rehabilitation and anxiety-reducing interventions after aSAH can be helpful to enhance the outcome. As this is the first study on participation after aSAH, in the future more studies are necessary to confirm our findings. Moreover, to improve our understanding of participation after aSAH, future studies should consider other factors as predictors of the level of participation such as PTSD symptoms, social support, personality characteristics, coping strategies, and fatigue.[30-32] In addition, it would be interesting to know more about the level of participation and satisfaction with participation in the longer term after aSAH.

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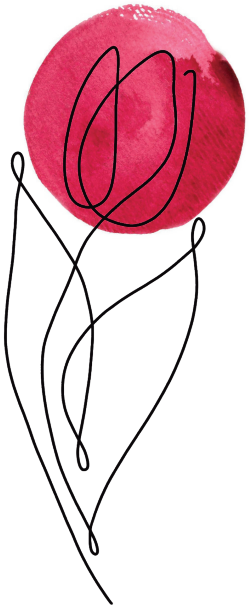
CHAPTER 8

Course of Participation after Subarachnoid Hemorrhage



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ABSTRACT

Introduction

The study aimed to investigate participation problems in patients with subarachnoid hemorrhage (SAH), and the course of participation between 3 and 12 months post-SAH, and to identify determinants of this course.

Methods

This is a prospective cohort study. The study was done in the SAH outpatient clinic at the University Medical Center Utrecht. Subjects included patients independent in activities of daily living who visited the SAH outpatient clinic for a routine follow-up visit 3 months after the event. Participation was assessed using the restrictions scale of the Utrecht Scale for Evaluation of Rehabilitation-Participation at 3, 6, and 12 months post-SAH. Repeated measures analysis of variance was conducted to identify possible determinants of participation (demographic and SAH characteristics, mood, and cognition).

Results

One hundred patients were included. Three months after SAH, the most commonly reported restrictions concerned work/unpaid work/education (70.5%), housekeeping (50.0%), and going out (45.2%). Twelve months post-SAH, patients felt most restricted in work/unpaid work/education (24.5%), housekeeping (23.5%), and chores in and around the house (16.3%). Participation scores increased significantly between 3 and 6 months, and between 3 and 12 months, post-SAH. The course of participation was associated with mood, cognition, and sex, but was in the multivariate analysis only determined by mood ($F(1, 74) = 18.31$, $p < 0.001$, partial eta squared: 0.20), showing lower participation scores at each time point for patients with mood disturbance.

Conclusions

Participation in functionally independent SAH patients improved over time. However, 1 out of 3 patients (34.9%) still reported one or more participation restrictions 12 months post-SAH. Mood disturbance was negatively associated with the course of participation after SAH.

INTRODUCTION

Most patients with subarachnoid hemorrhage (SAH) regain functional independence.[1,2] In case of good functional outcome, it is easily assumed that no aftercare will be necessary and these patients are usually discharged from the hospital without systematic follow-up. However, these patients may nevertheless experience restrictions in participation.[2,3] Participation is defined by the International Classification of Functioning, Disability and Health as "involvement in a life situation".[4] It is a broad concept that covers participation in paid and voluntary work, education, household tasks, leisure activities, interpersonal relationships, and community life. Participation is shown to be related to the quality of life (QoL) of stroke patients.[5] Most studies on outcomes after SAH have focused on QoL and employment. It has been shown that patients with aneurysmal SAH perceive reduced QoL.[2] In addition, not being able to return to work has been associated with reduced QoL.[3] In SAH research, relatively little attention has been paid to other domains of participation, such as leisure activities and interpersonal relationships. This is remarkable as optimal social participation is a primary aim of SAH care and many patients are not able to return to work. Knowledge of experienced participation problems in functionally independent patients with SAH may help increase clinician's awareness of these problems in rehabilitation care and help them set appropriate rehabilitation goals for this group.

The first aim of the present study was to investigate the experienced participation restrictions in functionally independent patients with SAH at 3, 6, and 12 months post-SAH. The second aim was to identify the factors that determine the course of participation restrictions. Knowledge about these factors may help clinicians tailor treatment at an early stage after SAH.

METHODS

Patients

In the University Medical Center Utrecht (UMC Utrecht), all patients with SAH who are discharged home or referred for inpatient rehabilitation to a rehabilitation center or rehabilitation ward of a nursing home are invited for a regular follow-up visit 3 months after SAH. In this study, patients included the following: (1) those who visited the SAH outpatient clinic between February 2010 and February 2011; (2) those who suffered from SAH caused by a ruptured aneurysm as confirmed by computed tomography, magnetic resonance, or conventional angiography, or in case no aneurysm was found, when an aneurysm was the presumed cause of the hemorrhage; and (3) those who were independent in activities of daily living (ADL), as shown by a maximum score of 20 on the Barthel Index.[6]

Procedure

All patients were seen by a specialized SAH nurse, a neuropsychologist, and a rehabilitation physician. Prior to their visit to the hospital, patients were sent a postal questionnaire that includes measures of participation and mood. Their responses were discussed during the follow-up visit. The same postal questionnaire was sent at 6 and 12 months after SAH. The study was approved by the UMC Utrecht Medical Ethics Committee.

Outcome Measurement

Participation was assessed using the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P).[7] This measure consists of 31 items, covering 8 out of 9 activities and participation chapters of the International Classification of Functioning, Disability and Health, and assesses 3 aspects of participation: frequency, experienced participation restrictions, and satisfaction with participation. The USER-P is a reliable,[7] valid,[8] and responsive[9] measure of participation in rehabilitation outpatients. In this study, only the restrictions scale was used, which consists of 10 items asking for experienced restrictions with participation as a result of SAH, for example restrictions in outdoor activities. Item scores range from 0 (not possible at all) to 3 (no difficulty at all), with a "not applicable" option for each item. The sum score of the scale is converted to a score on a 0-100 scale. Higher scores indicate good levels of participation (less restrictions).

Possible Determinants

Data on demographic and SAH characteristics were obtained from the SAH database of the Department of Neurology and Neurosurgery of the UMC Utrecht, and included sex, age, educational level, residence, and independence in ADL measured using the Barthel Index.[6] Educational level was scored according to Verhage classification system[10] and dichotomized as low or intermediate (0-5) and high (6-7; college, university). The SAH characteristics included location of aneurysm, clinical condition on admission (World Federation of Neurological Surgeons scale),[11] type of intervention (clipping or coiling), and presence of complications such as rebleeding, ischemia, and hydrocephalus.

To measure mood, the Hospital Anxiety and Depression Scale was used at 3 months post-SAH.[12] The total score on the Hospital Anxiety and Depression Scale with a cut-off score of 10/11 was used in all analyses because the anxiety and depression scores were strongly correlated, and the total score showed a better balance between sensitivity and positive predictive value in identifying cases of psychiatric disorder.[13]

A brief cognitive assessment was administered by the neuropsychologist to screen the main cognitive domains (memory, language, attention, executive functioning, visuospatial functioning, and orientation; see Supplementary file S4.1.2 of Chapter 4). This assessment contains 18 items with 3 possible scores for each item: 0 (unimpaired), 1 (mildly impaired), or 2 (severely impaired). The sum score of all items (range: 0-36) reflects overall cognitive impairment. In this study, the median score (4) was used as the cut-off score for impaired cognitive functioning.

Statistical Analyses

Data were analyzed with SPSS statistical package version 21.0 (IBM Corp., Armonk, NY). Descriptive statistics were used to describe the demographic data, SAH characteristics, mood, and cognition.

To investigate in which domains most participation restrictions were perceived, the item scores of the USER-P restriction scale were dichotomized. "Not possible" and "with assistance" were defined as "restriction," and "with difficulty" and "without difficulty" were defined as "no restriction." "Not applicable" answers were scored as missing values. To evaluate change in individual participation domains, the USER-P item scores at 3, 6, and 12 months post-SAH were compared using the Friedman test. Post-hoc analyses (3 with 6 months and 3 with 12 months) were conducted using the Wilcoxon signed-rank test because these comparisons were considered the most relevant to clinicians. To reduce the risk of chance findings, a p-value of 0.005 (0.05 divided by 10 restriction scale items) was considered statistically significant.

The total participation scores at T0, T1, and T2 were compared using the Friedman test and Wilcoxon signed-rank test. Effect sizes were calculated by dividing the z-value by the square root of N and interpreted using Cohen's criteria: 0.1 = small effect, 0.3 = medium effect, and 0.5 = large effect.[14] To determine which factors were associated with the course of participation, repeated measures analysis of variance was conducted. Candidate factors were sex, age, educational level, aneurysm location, World Federation of Neurological Surgeons scale score on admission, type of intervention, presence of complications, mood disturbances, and cognitive impairments. Possible determinants that were bivariately associated with participation ($p < 0.10$) were included in the multivariate analysis. In the multivariate analysis, a p-value of <0.05 was considered statistically significant. To calculate the strength of the association, the partial eta squared value was calculated and interpreted using Cohen's criteria: 0.01 = small effect, 0.06 = moderate effect, and 0.14 = large effect.[14]

RESULTS

Between February 2010 and February 2011, 231 patients suffered SAH and were admitted to the UMC Utrecht. Of these, 65 patients (28.1%) died. One hundred twenty-eight SAH patients visited the outpatient clinic of the UMC Utrecht for a regular follow-up visit 3 months after SAH. Of these, 100 patients met the inclusion criteria. At 3, 6, and 12 months post-SAH, USER-P data were available in 99, 97, and 88 patients, and a total score could be computed for 97, 95, and 88 patients, respectively.

At the time of their visit to the outpatient clinic, 80 patients (80.0%) were living at home, 14 (14.0%) were admitted to a rehabilitation center, 4 (4.0%) were staying at a rehabilitation ward of a nursing home, and 2 (2.0%) were staying elsewhere. Other characteristics of the included patients are summarized in Table 8.1.

Table 8.1 Characteristics of patients with SAH 3 months post-SAH (n=100).

Demographic characteristics	n	%
Sex women	66	66.0
Age in years, mean (SD)	54.8 (11.9)	
Range	20-83	
Educational level		
Low/intermediate	68	68.0
High	29	29.0
Unknown	3	3.0
SAH characteristics		
Mean follow up after SAH, weeks (SD)	10.5 (3.5)	
Location of aneurysm		
Internal carotid artery	3	3.0
Anterior communicating artery / pericallosa	38	38.0
Middle cerebral artery	16	16.0
Posterior communicating artery / vertebrobasilar arteries	22	22.0
Other	4	4.0
No aneurysm found	17	17.0

Table 8.1 Continued.

WFNS on admission		
I, GCS 15, no focal lesions	58	58.0
II, GCS 13-14, no focal lesions	26	26.0
III, GCS 13-14, focal lesions	3	3.0
IV, GCS 7-12, focal lesions or not	8	8.0
V, GCS 3-6, focal lesions or not	3	3.0
Unknown	2	2.0
Type of intervention		
Coiling	41	41.0
Clipping	41	41.0
None*	18	18.0
Complications		
Rebleeding	2	2.0
Secondary ischemia	7	7.0
Hydrocephalus	14	14.0
Hydrocephalus and ischemia	4	4.0
Other	7	7.0
None	65	65.0
Unknown	1	1.0
Emotional and cognitive characteristics		
Total HADS score (n=96)		
Anxiety and Depression [0-42]		
Mean (SD	10.1 (8.5)	
n (%) score ≥ 11	33	34.4
n (%) score ≥ 11	33	34.4
Cognitive assessment (n=96)		
Cognitive impairments [0-36]°		
mean (SD)	5.4 (4.6)	
n (%) score ≥ 4	53	55.2

SAH: Subarachnoid haemorrhage. WFNS: World Federation of Neurological Surgeons scale. HADS: Hospital Anxiety and Depression Scale.

*In 17 patients no aneurysm was found. One patient had not been treated because of high risk: a basilar top aneurysm including both posterior cerebral arteries in the presence of bilaterally occluded carotid arteries.

°There were 88 complete neuropsychological assessments, incomplete cases were left out. Reasons for incomplete assessments were amongst others aphasia, fatigue and communication difficulties with non-native speakers.

Table 8.2 Course of participation after SAH measured by the USER-Participation Restriction scale.

	3 months post-SAH (n=99)		6 months post-SAH (n=97)		12 months post-SAH (n=88)	
Participation (restriction)	n=97		n=95		n=85	
Mean score (SD)	68.6 (24.6)		80.2 (20.5)		82.7 (20.2)	
Median score	71.4		83.3		90.0	
IQR	51.9 - 90.2		66.7 - 100		70.5 - 100	
Restriction scale items	n	n persisting problems (%)	n	n persisting problems (%)	n	n persisting problems (%)
Work/unpaid work/education	44	31 (70.5)	43	16 (37.2)*	49	12 (24.5)*
Housekeeping	86	43 (50.0)	86	23 (26.7)*	81	19 (23.5)*
Physical exercise	81	23 (28.4)	76	11 (14.5)*	77	10 (13.0)*
Going out	73	33 (45.2)	79	16 (20.3)*	72	10 (13.9)*
Outdoor activities	84	32 (38.1)	86	22 (25.6)*	81	10 (12.3)*
Chores in/around house	81	32 (39.5)	81	14 (17.3)*	80	13 (16.3)*
Leisure indoors	86	3 (3.5)	81	3 (3.7)	78	3 (3.8)
Visits to family or friends	92	25 (27.2)	92	9 (9.8)*	86	11 (12.8)*
Visits from family or friends	94	6 (6.4)	94	3 (3.2)	85	3 (3.5)
Telephone/computer contact	93	6 (6.5)	90	3 (3.3)	83	4 (4.8)

Participation (restriction) score: higher score indicates good level of participation (less restrictions). SD=standard deviation. IQR=interquartile range.

Restriction scale items: persisting problems = not possible or with help. "Not applicable" category was left out.

*= p <0.005 in Wilcoxon signed rank test (alpha=0.05/10 to correct for multiple testing), T1 and T2 compared to T0.

Participation

The item scores of the restriction scale at 3, 6, and 12 months post-SAH are shown in Table 8.2. The most commonly perceived restrictions after 3 months concerned work/ unpaid work/education (70.5%), housekeeping (50.0%), and going out (45.2%). At 12 months after SAH, patients felt most restricted in work/unpaid work/ education (24.5%), housekeeping (23.5%), and chores in and around the house (16.3%). In most domains, there was a significant decrease in perceived restrictions, indicating improvement in participation over time (Table 8.2).

Participation scores increased between 3 and 6 months, and between 3 and 12 months, post-SAH (Table 8.2). The Friedman test indicated that there was a statistically significant difference across the 3 time points ($\chi 2$ (2, n = 83) = 73.025, $p < 0.001$). Post-hoc analysis using the Wilcoxon signed-rank test revealed a statistically significant increase in the restriction score between 3 and 6 months ($z = -5.63$, $p < 0.001$), and between 3 and 12 months ($z = -6.14$, $p < 0.001$), with a medium effect size ($r = 0.41$ and $r = 0.47$, respectively).

Determinants of the Course of Participation

Repeated measures analysis of variance showed bivariate associations with the course of participation for mood ($p < 0.001$, partial eta squared = 0.29, large effect), cognition ($p = 0.006$, partial eta squared = 0.091, moderate effect), and sex ($p = 0.051$, partial eta squared = .046, small effect). In the multivariate analysis (n = 82), only mood was a significant factor (F (1, 74) = 18.31, $p < 0.001$, partial eta squared: 0.20), suggesting worse participation scores at each time point for patients with mood disturbance. The results are displayed in Figure 8.1.

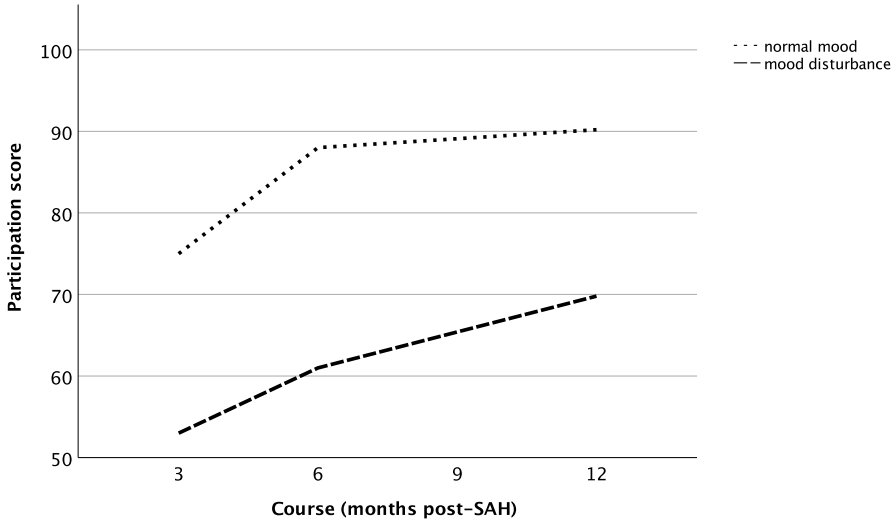

Figure 8.1 Participation scores for patients with normal mood and mood disturbance.

DISCUSSION

Participation of ADL-independent SAH patients improved during the first year post-SAH. However, a substantial group of 30 patients (34.9%) still reported one or more participation restrictions 12 months after SAH. Mood disturbance was negatively associated with the course of participation after SAH.

Strengths of this study are the assessment of different domains of participation, the description of its course over time, and the relatively large number of subjects with a relatively minor dropout rate. Limitations of this study are, first, that the data were gathered during standard patient care. Selection bias may be present because patients who did not come to the outpatient clinic 3 months after SAH could not be included. Second, it is unknown whether some patients received rehabilitation interventions during the follow-up period. Third, we only measured experienced participation restrictions. We did not measure actual (objective) participation.

It is difficult to compare our data with other study data because of the different definitions of participation and measures that have been used. In a follow-up study by Powell et al,[15,16] 52 patients with good neurologic recovery after surgery for SAH were assessed at 3, 9, and 18 months post-discharge using the Brain Injury Community

Rehabilitation Outcome-39 (BICRO-39) scale. The BICRO-39 is a health-related QoL measure that investigates independence in specific activities and frequency of socializing, productive employment, and psychological wellbeing. At 9 months post-discharge, over 35% of patients showed abnormally low levels of independence on the mobility scale (extended ADLs such as laundry and shopping), 50% reported abnormally low levels of independence in self-organization (planning, structuring domestic and personal routines, and managing finances), and 44% had resumed normal levels of productive employment (paid or voluntary employment, education and training, childcare). Eighteen months post-discharge, still almost half of the patients showed elevated dependence on others for domestic activities and organization and abnormally low levels of employment.[16] The results of this study in terms of restrictions in productive employment are in line with our findings.

In another study by Hop et al,[17] functional outcome was assessed in 64 SAH patients at 4 and 18 months post-SAH by means of the modified Rankin Scale (mRS), Short-Form-36 (SF-36), and Sickness Impact Profile (SIP). Functional outcome, as measured by the mRS, improved significantly between 4 and 18 months post-SAH. There was, however, no significant improvement over time in the "social functioning" domain of the SF-36. On the SIP, a significant difference was found only for the household management subdomain. The authors state that the sensitivity to detect changes in health status over time is believed to be limited for the SIP. Compared with the mRS, SF-36, and SIP, the USER-P gives more insight into the domains of participation in which patients feel restricted.

The most commonly perceived restrictions concerned work/unpaid work/education, despite a considerable decline in perceived restrictions between 3 (70.5%) and 12 months (24.5%) post-SAH. Return to work after acquired brain injury has been investigated by other researchers. A systematic review in 2009 concluded that about 40% of people with traumatic or nontraumatic brain injury were able to return to work after 1 or 2 years.[18]

In addition, a substantial proportion of people with acquired brain injury who returned to work were not able to sustain their job over time. In the previously mentioned studies on SAH,[15,16] almost half of the patients showed abnormally low levels of employment 18 months post-discharge. In other studies, with varying follow-up between 1 and 6 years, two thirds of previously employed SAH patients returned to work.[3,19-21] The findings of these studies are in line with our results, although we did not measure actual employment status. Experienced restrictions in work and education 12 months post-SAH seem to be lower than actual employment status as reported in these studies.

This might be explained by including only ADL-independent patients. Another possible explanation is that SAH patients who lost their job could have chosen the "not applicable" answer on this item. This category was left out in further analyses. What this study adds to previous knowledge is the subjective (perceived) restrictions in participation.

This study also shows that mood disturbance at 3 months post-SAH was negatively associated with the course of participation. Anxiety and depression are a common problem after SAH and seem to remain present over the first years after SAH.[15,16,22,23] The prevalence of mood disturbance in our study is in line with previous studies. In relation to social participation, Morris et al[23] found that anxiety and depression were associated with reduced social activity ("going out") and reduced ability to return to previous work. Vilkki et al[21] also found that emotional impairments were associated with decreased social activity. By contrast, in the previously mentioned study by Powell et al, very little variance in outcome was predicted by mood.[15,16] In our study, with a shorter follow-up period, mood disturbance at 3 months post-SAH was negatively associated with the course of participation. This is clinically relevant because early recognition and treatment of mood disturbance thereby may improve participation. A recent meta-analysis showed a medium effectiveness (effect size: 0.69; 95% CI 0.29 to 1.09) of psychological interventions on depressive symptoms in long-term rehabilitation after acquired brain injury.[24]

Cognition was bivariately, but not in the multivariate analysis, associated with the course of participation post-SAH. Relationships between cognition and participation after SAH have been examined in a few earlier studies.[15,16] In these studies, no association was found between cognitive impairment and participation. However, 1 year post-stroke, poor cognitive function was associated with reduced social participation.[25]

This study shows that a considerable number of people with SAH who are ADL-independent nevertheless experience participation restrictions. Clinicians should be aware of this and should pay attention to possible mood disturbances, because in this study mood disturbance was negatively associated with the course of participation. Early rehabilitation interventions may improve participation and may contribute to a better QoL, but the effectiveness of such interventions is subject to further research.

CLINICAL MESSAGES

- Participation of ADL-independent SAH patients improved during the first year post-SAH.
- However, 34.9% of patients still reported one or more participation restrictions 12 months post-SAH.
- Mood disturbance was negatively associated with the course of participation.
- Early interventions for mood disturbances may improve participation after SAH.

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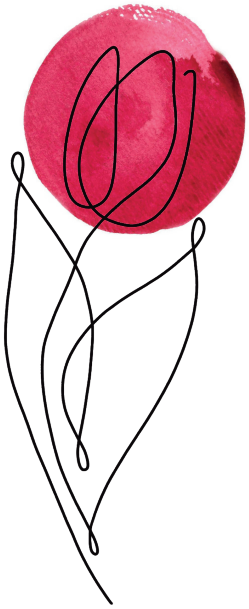
CHAPTER 9

General discussion



GENERAL DISCUSSION

The general objective of this thesis was to better understand the wide variety of cognitive and psychosocial outcomes for ADL-independent aSAH patients. We investigated factors related to cognitive complaints (subjective) and cognitive functioning (objective) 3 months after ictus. Moreover, we explored the course of symptoms of posttraumatic stress disorder (PTSD) and its determinants as well as the level of social participation during the first year after aSAH. In this final chapter the main findings of this thesis, methodological considerations, clinical implications and recommendations for future research are discussed.

MAIN FINDINGS

PART I: Determinants of cognitive outcomes after aSAH

In line with previous research,[1,2] more than 80% of the ADL-independent aSAH patients in our studies reported cognitive complaints and there were cognitive deficits in around half of the patients 3 months after ictus. Both complaints and deficits involve various cognitive domains. To get better insight into the cause of cognitive deficits after aSAH, we first aimed to elucidate the impact of the initial aSAH on cognition. We investigated whether cerebral perfusion within the first 24 hours after ictus was related to cognitive functioning 3 months post-aSAH. Although the acute increase in intracranial pressure and, as a result, the decrease in cerebral blood flow is thought to be one of the key factors of early brain injury after aSAH,[3] we found no effect of cerebral perfusion on cognitive functioning (**Chapter 2**). One of the explanations of this result might be that we missed the peak of the increase in intracranial pressure and the corresponding dip in cerebral blood flow, because these are strongest in the first minutes after aSAH.[4] In clinical practice it is, however, not feasible to scan a large series of aSAH patients so soon after ictus. Another explanation might be that it is not the initial decrease in cerebral blood flow, but secondary complications after aSAH that determine cognitive functioning after aSAH.[1] One of the secondary complications after aSAH is cerebral ischemia. We found that cerebral ischemia is a marker for poor cognitive functioning 3 months after aSAH. This effect appeared irrespective of the number and volume of the ischemic lesions (**Chapter 3**). The finding that both the number and volume of ischemic lesions have no effect on cognitive functioning confirms findings in the sole previous study we found on the relationship between ischemic lesions and cognitive outcome, including the number and volume of the lesions in their analysis.[5] It might be that, rather than the number and volume, the distribution of the ischemic lesions is more important to the differences in cognitive functioning after aSAH.[6] Because of the large variety in locations of ischemic lesions after aSAH and the limited power in our sample, we were not able to test this hypothesis in our study.

In order to prevent patients from secondary ischemia after aSAH, treatment with a neuroprotective agent, such as magnesium sulfate, has been extensively investigated.[7] Magnesium sulfate has no protective effect on functional outcome, when it is assessed by handicap scales.[8] Because of the relationship between cerebral ischemia and poor cognitive functioning, we hypothesized that magnesium sulfate might be beneficial for cognitive outcomes after aSAH, which is a subtler marker than handicap scales. In a sub-study of the randomized controlled Magnesium in Aneurysmal Subarachnoid Hemorrhage trial (MASH-II)[8] we found that there was no effect of magnesium sulfate on cognitive functioning after aSAH (**Chapter 4**). Despite our use of a more extensive and sensitive type of outcome compared to what has been reported in the literature (neuropsychological examination instead of handicap scale), our results do not change the previous conclusions that there is no indication to treat aSAH patients with magnesium sulfate in order to improve clinical outcomes.

Cerebral ischemia is not the only neurological complication after aSAH. Acute hydrocephalus is a frequent complication that also might be related to cognitive functioning after aSAH.[9-11] Acute hydrocephalus has a negative effect on cerebral perfusion in the acute phase, especially in the vicinity of the ventricles.[12] In line with previous studies, we found that cognitive functioning is not globally affected by ventricular size. We demonstrated, however, that memory, in particular, is vulnerable to enlarged temporal horns (**Chapter 5**). This effect might be explained by pressure of the temporal horns on the hippocampus. This anatomical structure is located next to the temporal horns and is crucial in memory function.[13] The results of our study show that the effect of enlarged temporal horns on cognitive functioning is not only specific for memory function, but it is also small. This means that although its contribution to the variability of cognitive functioning after aSAH is significant, it is also limited. Moreover, it appeared that at an individual level, the volume of the temporal horns does not distinguish between patients with and without memory impairments.

In both of the above studies on the role of cerebral ischemia and on the impact of enlarged ventricles on cognitive outcome, we focused not only on cognitive functioning, but also took patients' own experience about their cognitive functioning (cognitive complaints) into account. In contrast to the effects of cerebral ischemia on cognitive functioning, no effect of this neurological complication on cognitive complaints was found (**Chapter 3**). With respect to the ventricular volume, we found, however, similar to the effect on memory functioning, a small effect of the volume of the temporal horn on memory complaints (**Chapter 5**). Previous studies have shown that subjective measures of cognition (complaints) poorly match objective measures of cognitive outcome (functioning).[1,14,15] In addition, our findings in this thesis (**Chapter 3 & 5**) suggest that the overlap between

cognitive functioning and cognitive complaints might differ across different cognitive domains. In general, patients can give a good estimation of their memory functions based on daily experiences, but other cognitive functions, such as executive functions or mental speed appear harder for patients to judge from daily practice. This is in line with previous literature that shows that the level of self-awareness about one's own cognitive abilities is domain-specific.[16]

In summary, some of the variance in cognitive functioning after aSAH can be explained by the presence of cerebral ischemia during clinical course and, with respect to memory functions, the volume of the temporal horns in the (sub)acute phase after aSAH also plays a modest role. In an attempt to elucidate the impact of the initial aSAH, we did not find an effect of cerebral perfusion within the first 24 hours after ictus on cognitive functioning after aSAH. In addition to previous literature, these results help us to better understand what factors determine cognitive functioning and which factors do not significantly contribute to cognition after aSAH. However, a considerable amount of the variance in cognitive functioning is still not understood. This also applies to cognitive complaints after aSAH. With the exception of a small and memory-specific effect of the volume of temporal horn in the (sub)acute phase after aSAH, we found no factors that determine cognitive complaints after aSAH. Based on what is known about determinants of cognitive complaints after aSAH from the literature, much of the variance in cognitive complaints is still unexplained.[1]

PART II: Determinants of psychosocial outcomes after aSAH

The experience of an aSAH can be traumatic and in some patients can lead to PTSD.[17-19] In **Chapter 6** we showed that there is also substantial heterogeneity in the course of PTSD symptoms in the first year post-aSAH. Almost half of the patients experienced symptoms indicative of PTSD at one or at several time points in the first year after aSAH. In the total study population, there were signs of recovery in 15% of patients after symptoms indicative of PTSD at the initial assessment, and for almost similar proportions of patients there was a stable pattern (9%) or delayed symptoms indicative of PTSD (13%). This latter pattern, in which patients initially do not experience PTSD but develop PTSD in a later stage after aSAH, has not yet been described. The reason for this might be that, in contrast to previous studies,[20,21] we not only analyzed changes in PTSD symptoms at the group level, but also studied changes in PTSD symptoms over time at the individual level. Clinical outcome measures, such as demographics, aSAH characteristics, cognitive outcomes and the personality trait neuroticism appeared not to be related to the course of symptoms indicative of PTSD. Although, based on our study, we can exclude the influence of several factors, the cause of the heterogeneity in the course of PTSD symptoms in the first year post-aSAH is still unclear.

In **Chapters 7 & 8** we focused on the level of (social) participation of ADL-independent aSAH patients and its determinants. Six months after aSAH almost two-thirds of the aSAH patients (64%) reported one or more restrictions in participation and around the same proportion of patients reported dissatisfaction about their level of participation (**Chapter 7**). Most reported restrictions included housekeeping, chores in and around the house, physical exercise, outdoor activities and work or education. Although dissatisfaction with participation was to a large extent reported in relation to the same type of activities as those for which the patients experienced restrictions, some differences between the restrictions in participation and dissatisfaction about these activities were also found. For example, some patients reported restrictions regarding visits from or to friends and family but were nevertheless satisfied with these relationships. The level of restrictions and dissatisfaction with participation after an aSAH is determined by symptoms of anxiety and cognitive complaints. One in every five patients in our studies reported severe levels of anxiety 3 months after aSAH. This prevalence of anxiety symptoms and its relationship with reduced levels of participation are both in accordance with previous findings.[22] With respect to the course of participation, we found an improvement during the first year after aSAH (**Chapter 8**). However, at 12 months, one third of patients (35%) still experienced one or more restrictions in participation. In line with the level of participation, the course of participation restrictions during the first year after aSAH appeared to be determined by mood disturbances.

METHODOLOGICAL CONSIDERATIONS

All of the data used in the studies presented in this thesis were derived from clinical care as usual. Patients were selected from the subarachnoid hemorrhage outpatient clinic of the UMCU, where patients are invited who are discharged from hospital after an aSAH to a home or a rehabilitation institution on a temporary basis. As a result, only ADL-independent aSAH patients were included in our studies. Although these patients have good functional outcomes, they have considerable cognitive deficits, emotional distress and are hampered in their daily life, which makes studying the concepts of cognitive and psychosocial outcomes in this subgroup particularly relevant. Because one of our goals was to determine what pathophysiological events after aSAH are related to cognitive outcome after aSAH, we deliberately chose to include only patients with aneurysmal SAH's and not patients with a non-aneurysmal SAH such as a perimesencephalic SAH or a traumatic SAH. Because of these selection criteria, our results cannot be generalized to ADL-dependent patients and/or patients with a non-aneurysmal SAH.

The advantages of the clinical based character of our studies are that it allowed us to do longitudinal studies and it makes our results translate very well to daily clinical practice. It did,

however, also lead to some limitations. In order to improve medical health care, the protocol of cognitive and psychosocial assessments, for example, was changed twice during our study period. Moreover, because aSAH patients often experience fatigue, the time available for assessment during their visits to the hospital was also limited. Within each of the protocols of the neuropsychological assessments, tests of as many of the main cognitive domains as possible were included. The cognitive assessments were therefore more extensive compared to frequently used cognitive screening instruments such as the Mini-Mental-State-Examination (MMSE), Montreal Cognitive Assessment (MoCA) or Telephone Interview for Cognitive Status (TICS). Because of limited time, some domains (such as social cognition) were not or less extensively included in our protocols. Moreover, for the measurement of emotional disturbances after aSAH (PTSD, anxiety and depression) we used self-report questionnaires. Although these measures are well validated,[23,24] they can lead to an overestimation of these symptoms compared to diagnosis based on a formal psychiatric interview.[25] For the level of participation we focused on restrictions to and satisfaction with (social) activities in daily life. This information helped us prioritize which participation activities to focus on in rehabilitation. It is, however, important to realize that both participation restrictions and satisfaction are subjective levels of participation, which are often poorly related to actual frequencies (objective level) of participation.[26] Another limitation of our studies is that the sample sizes of our studies were relatively small. Taking into account the low incidence of aSAH and our selection of only ADL-independent aSAH patients, the number of patients included in our samples can, however, be considered substantial compared to samples in the literature. Because of the limited power in our sample, in some studies we needed to summarize measures in order to adjust for (**Chapter 2**) or exclude variables for adjustment (**Chapter 4**) or we could not perform a subgroup analysis (**Chapter 3**). This might have led to an underestimation of a potential association or excluded the possibility of specifying our findings. Moreover, to retain enough power in the study to measure the course of PTSD (**Chapter 6**), multilevel analyses was used. Latent growth mixture modeling might be more optimal for analyzing these longitudinal PTSD data, but this requires a large sample size, which, given the prevalence of aSAH, will be difficult to achieve.

CLINICAL IMPLICATIONS

Based on the results of the studies reported in this thesis, several implications for clinical practice can be made. With respect to the medical care during the clinical course of aSAH patients, our study showed that treatment of aSAH patients with magnesium sulfate is not indicated to improve clinical outcomes (**Chapter 4**). Moreover, there is also no indication of aggressive drainage in patients with enlarged ventricles, but without clinical symptoms of hydrocephalus in the acute phase after aSAH, in order to protect patients from cognitive decline (**Chapter 5**).

In addition to these indications on the medical care during clinical course, this thesis also provides recommendations for medical care during follow-up of aSAH patients. According to the vision of a committee of medical specialists (Vision document 'Medical Specialist 2025'), in future medical care, clinicians should besides the medical treatment, also help patients resuming their (social) role in the family and in society.[27] In line with this, the International Classification of Functioning, Disability and Health, states that improving patients' quality of life requires a patient tailored and holistic approach in which, besides physical outcomes, attention must also be paid to cognitive and emotional functioning as determinants for activities and social participation (see the ICF model in Figure 9.1).[28] The studies in this thesis illustrate the claim that a multidisciplinary approach, in which the neurosurgeon and/or neurologist, rehabilitation physician, neuropsychologist, and a nurse practitioner specialized in SAH work can together help to achieve these goals.

When aSAH patients are ADL-independent and are discharged from the hospital to home, information about what to expect from recovery and advice about resuming daily activities can help patients to cope adequately with possible cognitive deficits. Clinicians should in this respect take into account that patients with one or more ischemic lesions during clinical course have an increased risk of cognitive deficits which can remain for at least several months post-aSAH (**Chapter 3**). In line with previous literature,[29] we recommend evaluating cognitive and emotional outcome at 3 months after aSAH. After 3 months, ADL-independent aSAH patients often try to regain their pre-morbid (complex) activities in daily life (e.g. return to work) and are (again) confronted with the impact of cognitive deficits (even when these are subtle). In addition to the cognitive evaluation, we advise measuring both health-related quality of life and the level of participation and to what extent these are changed after an aSAH. Measuring cognitive outcome and participation can reveal concrete goals for rehabilitation (**Chapter 7**). It provides guidance on what problems related to complex activities to focus on. With respect to the level of participation, is important to not only ask patients about their restrictions in participation, but also to get insight into what activities in daily life they are dissatisfied about (**Chapter 7**). Moreover, a partner's or other relative's evaluation should be taken into account and/or objective measures of participation (frequency scale) should be used. This also accounts for cognitive outcome; we recommend to both ask patients about their own experience (subjective) and to perform a formal neuropsychological examination (objective). These measures should cover the main cognitive domains (memory, attention, executive functioning, social cognition, language, mental speed, visuospatial functioning). Because there are large variations in the severity of cognitive deficits, neuropsychological tests should be sensitive to both severe and to more subtle cognitive decline (e.g. avoiding floor and ceiling effects).

With respect to emotional outcomes, we recommend measuring symptoms of depression and anxiety as well as symptoms of PTSD. Because some aSAH patients do not experience PTSD symptoms in the first months after aSAH, but later on (delayed), PTSD should be assessed at various time points in the initial year post-aSAH (**Chapter 6**). If symptoms indicative of PTSD are present, patients should be referred for (psycho)therapy. This also applies to symptoms of anxiety and depression. Not only because this might improve patient's mood after aSAH, but also because interventions for anxiety and depression can be helpful in enhancing the level of participation after aSAH (**Chapter 7 & 8**).

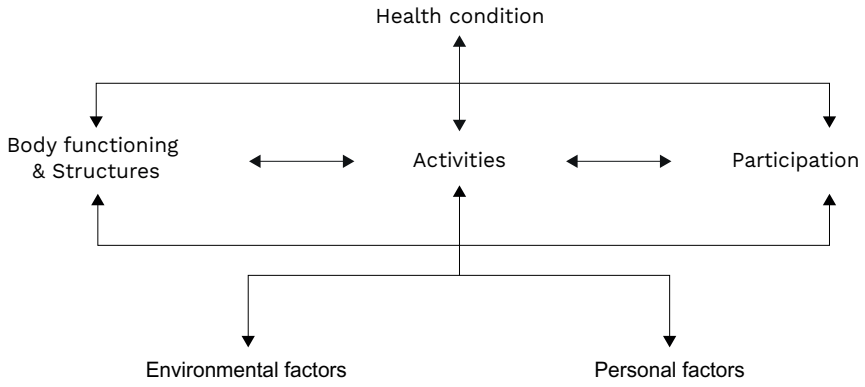


Figure 9.1 Bio-psycho-social model of the International Classification of Functioning, Disability and Health (ICF)[28]

RECOMMENDATIONS FOR FUTURE RESEARCH

To examine the cognitive sequelae after an aSAH, an extensive neuropsychological examination that includes tasks for the main cognitive domains that are both specific and sensitive to cognitive decline, should be used. In 2015, a Swiss study group made a nationwide call for a uniform neuropsychological assessment after aneurysmal subarachnoid hemorrhage which included recommendations on specific neuropsychological tests.[29] These traditional neuropsychological tests are designed to investigate the fundaments of cognitive functioning and help clinicians to find the underlying (cognitive) source of problems in daily life. Other factors, such as fatigue or distraction by stimuli which are not of interest, are eliminated as far as possible. This is valuable and necessary information. However, this neuropsychological examination does not always translate very well to activities in daily practice in which combinations of different cognitive fundaments (multitasking) are required and irrelevant stimuli (sounds or visual stimuli) may be overwhelming and need

to be filtered out. In daily life, patients often get overstimulated and decisions on what information to use and what to filter out needs to be taken fast. In the prediction of patients' daily life functioning after aSAH, it could be interesting to extend the traditional neuropsychological tests with more dynamic tasks that resemble daily life situations, for example, with the use of virtual reality simulation.[30]

Moreover, because brain injury can be subtle in ADL-independent aSAH patients, in the search for pathophysiological markers of cognitive functioning in this subgroup, we recommend the use of sensitive imaging techniques in future studies. In clinical care of aSAH patients, computerized tomography (CT) is most often used. However, microstructural white matter abnormalities are not always visible on clinical CT and can be better detected with Diffusion Tensor Imaging (DTI).[31] A recent DTI study showed that, in the subacute phase after aSAH, patients have temporary white matter abnormalities that are associated with cognitive impairment 3 months post-aSAH.[32] Future studies are needed to determine whether this relationship is causal. It can also be interesting to focus on the locations of both ischemic lesions and microstructural white matter abnormalities, because these might be important for the nature and severity of the cognitive deficits after aSAH.[6] In addition, network connectivity studies might help to indicate to what extent hubs are disturbed and, as a result, the integrity of functional brain networks is reduced and how this relates to cognitive functioning after aSAH.[33]

Besides the sensitivity of both neuropsychological examination and imaging techniques, the timing of these measurements is also important. Some of the brain injuries follow directly after the rupture of the aneurysm,[3] while other (secondary) complications can occur up to several days after aSAH[34] or even remain until the chronic phase.[35] In our study on the effect of enlarged ventricles on cognitive functioning after aSAH, for example, we focused on the ventricular volume in the (sub)acute phase. Future studies could indicate how the ventricular volume develops over time and how delayed or chronically enlarged ventricles affect cognitive functioning after aSAH. With regard to cognitive functioning after aSAH, in this thesis all neuropsychological examinations were performed at 3 months post-SAH. More research should be conducted to get insight into the extent to which the pathophysiological processes resulting from an aSAH contribute to cognitive outcomes in the longer term.

Whereas this thesis focused specifically on the biological aspects of aSAH in order to understand the differences in cognitive functioning after aSAH, there are also studies that have found that psychological factors (e.g. symptoms of anxiety, PTSD or depression) play a role.[2] It could be interesting for future studies to combine findings from both medical and social sciences to see how factors from both perspectives relate to each other in determining

cognitive functioning after aSAH. Because it appeared for patients' own evaluation of their cognitive functioning that biological aspects of the aSAH are less relevant, in order to reveal the cause of cognitive complaints, we would recommend focusing more on psychological factors. As shown in a previous study, much of the variance in cognitive complaints after aSAH can be explained by depressive symptoms.[1] However, less is known about the effect of personality characteristics or coping strategies on cognitive complaints after aSAH.[36] As shown in a study on stroke these factors might play an important role in explaining cognitive complaints.[37] Moreover, based on the ICF model (Figure 9.1),[28] future studies should also include factors such as the role of the partner and social support of aSAH patients.

As for cognitive complaints, personality characteristics, coping strategies and social support might also play a role in the level of participation after aSAH. There are few studies on the level of participation after aSAH and so far, these factors have not been taken into account and might therefore be interesting for future research. With respect to PTSD symptoms, more research is needed to answer the question as to whether post-aSAH physical discomfort or psychical signs, which a patient might relate to the aSAH (e.g. a headache), are associated with symptoms of PTSD. According to the Enduring Somatic Threat (EST) model, PTSD symptoms due to a medical event are strongly associated with the ongoing consequences of the event.[38] It would be interesting to test this hypothesis in aSAH patients. Moreover, future studies should investigate PTSD symptoms in partners or other close relatives, too. As with relatives of stroke survivors, the sudden, unexpected, and life-threatening nature of the aSAH itself and the physical, cognitive, and psychological changes in the aSAH survivor, might also cause a traumatic stress reaction in people who are close to the aSAH survivor.[39]

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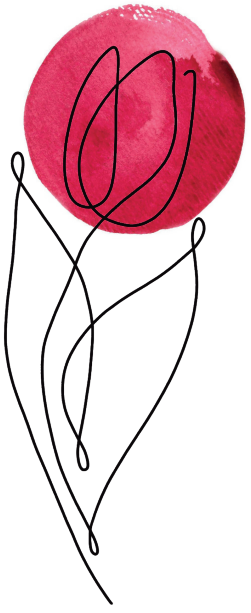
Samenvatting



SAMENVATTING

Een subarachnoïdale bloeding (SAB) is een bloeding in een ruimte rondom de hersenen (de subarachnoïdale ruimte). Een SAB ontstaat in een groot deel van de gevallen door een ruptuur van een intracranieel aneurysma, een bolvormige uitstulping van een slagader. We spreken dan van een aneurysmatische SAB (aSAB). De incidentie van dit type hersenbloeding is ongeveer 6 per 100.000 personen per jaar. Een aSAB komt voornamelijk voor bij relatief jonge mensen, met een gemiddelde leeftijd van 55 jaar. Het betreft een levensbedreigende aandoening: slechts 65% van de getroffenen overleeft een aSAB. Van de patiënten die de aSAB overleven is een klein deel (10-20%) na de aSAB onvoldoende in staat zelfstandig algemene dagelijkse levensverrichtingen (ADL) uit te voeren en wordt daarom opgenomen in een verpleeghuis of revalidatiecentrum. Het merendeel van de patiënten die een aSAB overleven zijn echter ADL-zelfstandig en gaan na ontslag uit het ziekenhuis naar huis. Ondanks dat deze ADL-zelfstandige aSAB patiënten fysiek goed hersteld zijn, hebben zij bij thuiskomst vaak veel moeite om hun leven weer volledig op te pakken. Veel patiënten rapporteren cognitieve klachten zoals mentale traagheid en verminderde geheugen- en aandachtfuncties. Ook komen depressieve klachten, angstklachten en/of posttraumatische stressklachten regelmatig voor na een aSAB. Deze cognitieve en emotionele klachten hebben een weerslag op het dagelijks functioneren van deze patiënten. Complexe activiteiten zoals werk, (financiële) administratie, huishouden en boodschappen doen zijn vaak lastig voor ADL-zelfstandige aSAB patiënten. Daarnaast geeft een deel van deze aSAB patiënten aan zich beperkt te voelen in het oppakken van hun rol in het gezin, relaties met familie en vrienden en/of participatie in de maatschappij. De ernst van de cognitieve en emotionele klachten en stoornissen van ADL-zelfstandige aSAB patiënten en de mate waarin zij beperkingen ervaren in het oppakken van hun (sociale) leven na de aSAB verschilt tussen aSAB patiënten. Dit proefschrift richt zich op de vraag welke factoren een rol spelen in de cognitieve, en psychosociale klachten en stoornissen van ADL-zelfstandige aSAB patiënten, met als doel handvatten te bieden voor de medische behandeling en (cognitieve) revalidatie van deze patiënten.

Determinanten van cognitief functioneren na een aSAB

In deel I is onderzoek gedaan naar determinanten van cognitieve klachten en cognitief functioneren na een aSAB. Hierbij ligt de focus op de invloed van verschillende pathofysiologische processen die (kunnen) optreden na een aSAB. In **hoofdstuk 2** is gekeken naar de relatie tussen cerebrale perfusie (doorbloeding van de hersenen) binnen de eerste 24 uur na een aSAB en cognitief functioneren 3 maanden na die aSAB. Alhoewel de acute verhoging van intracraniële druk, en als gevolg daarvan verlaging van cerebrale perfusie, gezien wordt als een van de belangrijkste oorzaken van vroege hersenschade na een aSAB, is er geen relatie tussen cerebrale perfusie en cognitief functioneren gevonden. Een

mogelijke verklaring hiervoor is dat we de piek in intracraniële druk en corresponderende dip in cerebrale perfusie na de aSAB hebben gemist, aangezien deze het meest uitgesproken is in de eerste minuten na een aSAB. Het is echter in de klinische praktijk onmogelijk om de cerebrale perfusie zo vroeg na de aSAB te onderzoeken.

Naast de initiële bloeding kunnen mogelijk ook secundaire neurologische complicaties van invloed zijn op het cognitief functioneren na een aSAB. Een veel voorkomende complicatie is cerebrale ischemie. In **hoofdstuk 3** tonen we aan dat cerebrale ischemie gedurende de klinische opname een indicator is voor verminderd cognitief functioneren 3 maanden na de aSAB. Dit effect blijkt niet beïnvloed te worden door het aantal en het volume van de ischemische laesies.

Om aSAB patiënten te beschermen tegen secundaire ischemie is veel onderzoek verricht naar neuroprotectieve behandelingen, bijvoorbeeld met magnesiumsulfaat. Ondanks positieve resultaten van pre-klinische en fase II-studies laat een eerdere gerandomiseerde klinische studie (MASH-II) geen effect zien van behandeling met magnesiumsulfaat op de klinische uitkomst van aSAB patiënten. In dit onderzoek is de klinische uitkomst gemeten met een handicap schaal (modified Rankin Scale). Deze schaal geeft een goede indruk van beperkingen in ADL en mobiliteit, maar (subtiele) cognitieve problemen worden hiermee niet of onvoldoende gedetecteerd. In een sub-studie van dit gerandomiseerd klinisch onderzoek hebben we daarom gekeken naar het effect van magnesiumsulfaat op het cognitief functioneren, gemeten met neuropsychologische tests (**hoofdstuk 4).** Ondanks het gebruik van meer uitgebreide en gevoeligere uitkomstmaten leiden onze resultaten niet tot verandering van de eerdere conclusie. Een behandeling met magnesiumsulfaat leidt niet tot verbetering van de klinische uitkomst (inclusief het cognitief functioneren) van aSAB patiënten en is daarom niet geïndiceerd.

Een andere neurologische complicatie die naast cerebrale ischemie frequent voorkomt na een aSAB is een hydrocephalus (waterhoofd). In **hoofdstuk 5** laten we zien dat het cognitief functioneren 3 maanden na de aSAB niet beïnvloed wordt door het algehele volume van de cerebrale ventrikels, maar dat wel specifiek het geheugen gevoelig is voor het volume van de temporaalhoorns. Dit kan mogelijk worden verklaard door de druk van de temporaalhoorn op de hippocampus, een anatomische structuur die naast de temporaalhoorn ligt en cruciaal is voor het geheugen. Het effect van de temporaalhoorn op het geheugen is significant, maar beperkt. Op individueel niveau kan op basis van het volume van de temporaalhoorns geen onderscheid worden gemaakt tussen patiënten met en zonder geheugenstoornissen. We concluderen daarom dat bij vergrote temporaalhoorns, maar afwezigheid van klinische symptomen, er geen indicatie is voor agressieve drainage.

In zowel de studie naar de invloed van cerebrale ischemie als de studie naar het effect van het volume van ventrikels op het cognitief functioneren na aSAB, hebben we niet alleen middels neuropsychologische tests naar cognitief functioneren gekeken, maar patiënten ook gevraagd of en in welke mate zij cognitieve klachten ervaren. In tegenstelling tot de negatieve invloed van cerebrale ischemie op het cognitief functioneren, vinden we geen relatie tussen deze neurologische complicatie en de door patiënten ervaren cognitieve klachten (**hoofdstuk 3**). Dit betekent dat aanwezige cognitieve klachten niet door deze neurologische complicatie kunnen worden verklaard (**hoofdstuk 3**). Wat betreft het volume van de ventrikels zien we dat patiënten specifiek meer geheugenklachten rapporteren naarmate het volume van de temporaalhoorns groter is (**hoofdstuk 5**). Dit komt overeen met het effect dat we vinden van het volume van de temporaalhoorns op de geheugenprestaties van aSAB patiënten. Bevindingen op basis van subjectieve maten van cognitief functioneren (cognitieve klachten) komen vaak beperkt overeen met de bevindingen van objectieve maten van cognitief functioneren (cognitieve tests). Onze resultaten suggereren dat de overlap tussen deze subjectieve en objectieve maten van cognitief functioneren mogelijk domeinspecifiek zijn. In het algemeen kunnen patiënten een goede inschatting geven van hun geheugenfuncties, maar het inschatten van andere cognitieve functies, zoals executieve functies of mentale snelheid, blijkt voor veel patiënten lastiger.

Concluderend moge het duidelijk zijn dat er niet één factor aan te wijzen is die verantwoordelijk is voor de cognitieve klachten en cognitieve stoornissen na een aSAB. Alhoewel het huidige proefschrift meer zicht geeft op de determinanten van cognitief functioneren na een aSAB, blijft een deel van de variantie in cognitief functioneren na een aSAB onverklaard. In dit proefschrift ligt de focus op de pathofysiologische factoren. Er zijn tevens onderzoeken die sterke aanwijzingen geven dat psychologische factoren (stemming, angst, PTSS) ook een rol kunnen spelen in het cognitief functioneren na aSAB. Er ligt een uitdaging voor toekomstig onderzoek om bevindingen van deze medische en psychologische onderzoeken samen te voegen. Hiermee kan mogelijk meer inzicht worden verkregen in hoe deze beide perspectieven zich tot elkaar relateren, en in welke mate deze factoren samen het cognitief functioneren na een aSAB beïnvloeden.

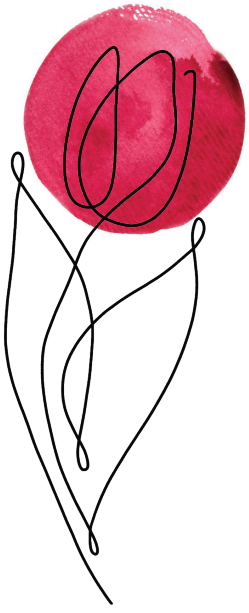
Determinanten van psychosociaal functioneren na een aSAB

Deel II van het proefschrift is gericht op de determinanten van psychosociaal functioneren na een aSAB. Meer specifiek is er gekeken naar welke factoren van invloed zijn op posttraumatische stressklachten en beperkingen in participatie na een aSAB, en het beloop van deze klachten in de tijd. Een kwart van de aSAB patiënten heeft last van posttraumatische stressklachten suggestief voor een posttraumatische stressstoornis (PTSS), zelfs tot 3 jaar na de aSAB. Alhoewel dit aantal op groepsniveau over de tijd gelijk blijft, zien we op individueel niveau veranderingen in het aantal klachten suggestief voor PTSS

over de tijd (**hoofdstuk 6**). Ongeveer de helft van alle aSAB patiënten heeft op een moment binnen het eerste jaar klachten suggestief voor PTSS. In 15% van de gehele studiepopulatie zien we dat symptomen suggestief voor PTSS in de eerste maanden, later in het jaar herstellen. Met bijna vergelijkbare percentages zien we daarnaast ook patiënten met een stabiel patroon van symptomen suggestief voor PTSS (9%) en patiënten die in eerste maanden geen of weinig PTSS-symptomen ervaren, maar waarbij later in het jaar de symptomen toenemen en wel suggestief voor PTSS zijn (13%). Omdat het moment waarop patiënten PTSS-symptomen na een aSAB kunnen ontwikkelen tussen patiënten verschilt, adviseren wij clinici om PTSS-symptomen op verschillende momenten gedurende het eerste jaar na de aSAB in kaart te brengen. Op deze manier kunnen clinici PTSS-symptomen tijdig signaleren en patiënten doorverwijzen voor (psycho)therapie. Klinische uitkomsten zoals demografische karakteristieken, aSAB karakteristieken, cognitief functioneren en kenmerken van een neurotische persoonlijkheidsstructuur blijken allen niet gerelateerd aan het beloop van symptomen suggestief voor PTSS. Alhoewel we aan de hand van onze studie veel factoren hebben kunnen uitsluiten, blijft onduidelijk welke factoren wél van invloed zijn op het beloop van PTSS na een aSAB. Volgens het aanhoudende-somatische-dreigingsmodel (Enduring Somatic Threat model) hangen PTSS-symptomen sterk samen met aanhoudende somatische klachten of signalen die patiënten associëren met de traumatische gebeurtenis. Het zou interessant kunnen zijn om binnen de aSAB-populatie verder onderzoek te doen naar deze hypothese.

In **hoofdstuk 7 & 8** is naar factoren gezocht die gerelateerd zijn aan de mate en het beloop van (sociale) participatie van ADL-zelfstandige aSAB patiënten. Zes maanden na de aSAB rapporteert ongeveer twee derde (64%) van de patiënten beperkingen in participatie en een vergelijkbare hoeveelheid geeft aan hierover ontevreden te zijn (**hoofdstuk 7**). Patiënten rapporteren de meeste beperkingen bij huishoudelijke taken en andere werkzaamheden in en rondom het huis, lichaamsbeweging, dagtochtjes en bij werk of opleiding. De mate van beperkingen in participatie en ontevredenheid over participatie wordt beïnvloed door cognitieve en angstklachten. Kijkend naar het beloop van participatie na een aSAB, zien we een verbetering gedurende het eerste jaar na de aSAB (**hoofdstuk 8**). Echter, 1 jaar na de aSAB ervaart nog steeds een derde van de aSAB patiënten beperkingen in participatie. De verbetering in participatie gedurende het eerste jaar is lager naarmate patiënten meer last hebben van stemmingsklachten. Cognitieve revalidatie en (psychologische) interventies gericht op angst- en stemmingsklachten kunnen behulpzaam zijn bij het verbeteren van de participatie van patiënten die een aSAB hebben doorgemaakt. Naast cognitieve en emotionele klachten zijn mogelijk ook andere psychosociale factoren van invloed op de mate van participatie na een aSAB. Voorbeelden hiervan zijn persoonlijkheid, coping strategieën en sociale steun. Toekomstig onderzoek is nodig om uit te wijzen in hoeverre deze factoren een rol spelen in participatie na een aSAB.

Dankwoord



DANKWOORD

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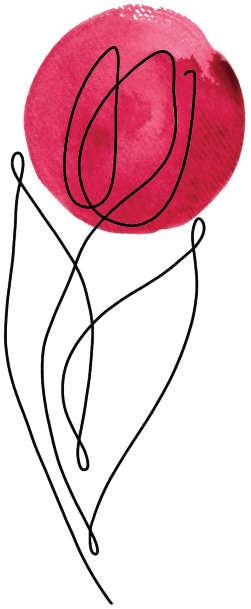
About the author



CURRICULUM VITAE

Irene Huenges Wajer was born on December 5th 1984 in Leiden, the Netherlands. She grew up in Berg en Terblijt and finished secondary school at Stella Maris College in Meerssen. In 2005 she started the study psychology at Utrecht University (UU), where her interest in neuropsychology developed. During the master's program 'Neuropsychology' she followed a clinical internship and performed a research project at the department Neurology & Neurosurgery of University Medical Center Utrecht (UMCU). After working for a year as a lecturer at the Psychology department of UU, she started working as a neuropsychologist at the UMCU. Here she was trained in 2011 and 2012 for Healthcare Psychologist (GZ-psycholoog) under supervision of dr. M.J.E. van Zandvoort. As part of this training she weekly assessed patients who survived a subarachnoid hemorrhage (SAH) at the SAH-outpatient clinic of the UMCU department of Rehabilitation. Following her clinical work at this outpatient clinic she started a PhD project in 2013 under supervision of prof. dr. G.J.E. Rinkel, prof. dr. M.J.A Visser-Meily and dr. M.J.E. van Zandvoort. Besides combining this PhD project with her clinical work as healthcare psychologist at the department of Neurology & Neurosurgery at the UMCU, she also continued her job as lecturer since 2013 at the department of Experimental Psychology of UU. Since 2017 Irene started a specialization training for Clinical Neuropsychologist, including an honors program (Topklas).

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