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NEUROSURGICAL FOCUS

Neurosurg Focus 54(4):E3, 2023

Successful weaning versus permanent cerebrospinal fluid diversion after aneurysmal subarachnoid hemorrhage: post hoc analysis of a Swiss multicenter study

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OBJECTIVE Acute hydrocephalus is a frequent complication after aneurysmal subarachnoid hemorrhage (aSAH). Among patients needing CSF diversion, some cannot be weaned. Little is known about the comparative neurological, neuropsychological, and health-related quality-of-life (HRQOL) outcomes in patients with successful and unsuccessful CSF weaning. The authors aimed to assess outcomes of patients by comparing those with successful and unsuccessful CSF weaning; the latter was defined as occurring in patients with permanent CSF diversion at 3 months post-aSAH.

METHODS The authors included prospectively recruited alert (i.e., Glasgow Coma Scale score 13–15) patients with aSAH in this retrospective study from six Swiss neurovascular centers. Patients underwent serial neurological (National Institutes of Health Stroke Scale), neuropsychological (Montreal Cognitive Assessment), disability (modified Rankin Scale), and HRQOL (EuroQol-5D) examinations at < 72 hours, 14–28 days, and 3 months post-aSAH.

RESULTS Of 126 included patients, 54 (42.9%) developed acute hydrocephalus needing CSF diversion, of whom 37 (68.5%) could be successfully weaned and 17 (31.5%) required permanent CSF diversion. Patients with unsuccessful weaning were older (64.5 vs 50.8 years, $p = 0.003$) and had a higher rate of intraventricular hemorrhage (52.9% vs 24.3%, $p = 0.04$). Patients who succeed in restoration of physiological CSF dynamics improve on average by 2 points on the Montreal Cognitive Assessment between 48–72 hours and 14–28 days, whereas those in whom weaning fails worsen by 4 points (adjusted coefficient 6.80, 95% CI 1.57–12.04, $p = 0.01$). They show better neuropsychological recovery between 48–72 hours and 3 months, compared to patients in whom weaning fails (adjusted coefficient 7.60, 95% CI 3.09–12.11, $p = 0.02$). Patients who receive permanent CSF diversion (ventriculoperitoneal shunt) show significant

ABBREVIATIONS aSAH = aneurysmal subarachnoid hemorrhage; DCI = delayed cerebral ischemia; EQ-5D = EuroQol-5D; EVD = external ventricular drain; HRQOL = health-related quality of life; IQR = interquartile range; IVH = intraventricular hemorrhage; LD = lumbar drain; MoCA = Montreal Cognitive Assessment; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; VPS = ventriculoperitoneal shunt.

ACCOMPANYING EDITORIAL DOI: 10.3171/2023.1.FOCUS2342.
SUBMITTED September 25, 2022. **ACCEPTED** January 17, 2023.
INCLUDE WHEN CITING DOI: 10.3171/2023.1.FOCUS22638.

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neuropsychological improvement thereafter, catching up the delay in neuropsychological improvement between 14–28 days and 3 months post-aSAH. Neurological, disability, and HRQOL outcomes at 3 months were similar.

CONCLUSIONS These results show a temporary but clinically meaningful cognitive benefit in the first weeks after aSAH in successfully weaned patients. The resolution of this difference over time may be due to the positive effects of permanent CSF diversion and underlines its importance. Patients who do not show progressive neuropsychological improvement after weaning should be considered for repeat CT imaging to rule out chronic (untreated) hydrocephalus.

Clinical trial registration no.: NCT03032471 (ClinicalTrials.gov)

https://thejns.org/doi/abs/10.3171/2023.1.FOCUS22638

KEYWORDS subarachnoid hemorrhage; Montreal Cognitive Assessment; delayed cerebral ischemia; stroke; neuropsychological outcome

Aneurysmal subarachnoid hemorrhage (aSAH) is a type of stroke associated with high rates of morbidity and mortality.[1] Despite continuous improvements in diagnostics, and in endovascular and surgical treatment, mortality attributable to aSAH remains high at approximately 30%–40%.[2] Hydrocephalus (often occlusive at first and later malresorptive) is a frequent complication after aSAH,[3,4] probably due to inflammatory reactions caused by the subarachnoid blood contributing to meningeal thickening and CSF blockage.[5–8]

In patients with ventricular enlargement and clinical signs of elevated intracranial pressure, CSF diversion is performed by insertion of an external ventricular drain (EVD) or lumbar drain (LD) in up to 75% of cases.[5,9,10] Given that CSF flow dynamics may normalize over time, some patients can be successfully weaned from CSF diversion. However, a substantive number of patients remain dependent on permanent CSF diversion, which in the majority requires insertion of a ventriculoperitoneal shunt (VPS).[11] Permanent VPS dependency has been associated with neurocognitive deficits and worse functional outcome,[12] which is suggested to be due to the underlying brain injury in patients requiring VPS and not to the VPS itself. In the past decades, functional and neuropsychological deficits caused by aSAH have received increased attention.[13–20] Nevertheless, little is known about differences in functional and neuropsychological outcome between successfully and unsuccessfully weaned patients after aSAH-related hydrocephalus.

Our aim was to assess differences in neurocognitive function, disability, and health-related quality of life (HRQOL) in patients with aSAH who have posthemorrhagic hydrocephalus, comparing successfully versus unsuccessfully weaned patients.

Methods

Patient Population

We conducted a post hoc, retrospective analysis on a data set of a prospective multicenter cohort (Montreal Cognitive Assessment–Delayed Cerebral Ischemia [MoCA-DCI] study).[17] Patients from centers collaborating in the Swiss SOS (Swiss Study on Aneurysmal Subarachnoid Hemorrhage) project were consecutively included between 2017 and 2020.[21–23] Inclusion criteria were as follows: confirmed aSAH on imaging; age ≥ 18 years; Glasgow Coma Scale score ≥ 13 points at 48–72 hours after aSAH; and fluent in either English, German, French, or Italian for the neuropsychological assessment. Exclusion criteria were as follows: arterial vasospasm on the initial angiography study; preexisting neurological or psychiatric diseases (including but not limited to dementia, multiple sclerosis, and bipolar disorder); follow-up not possible (mostly due to geographic reasons—e.g., patients living abroad); or requirement for a sedative or other medication within 72 hours that would interfere with the patient's consciousness and therefore evaluation.

Examinations and Outcome Measures

In general, patient evaluations followed Swiss national and international recommendations and were conducted serially at < 72 hours, 14–28 days, and approximately 90 days (3 months) after aSAH.[23–25] Study investigators were trained in the use and standardized application of outcome measures. Neurological status was evaluated using the National Institutes of Health Stroke Scale (NIHSS) at the same time points. The modified Rankin Scale (mRS) was used to classify disability, dichotomized into 0–3 for good and 4–6 for poor functional outcome. Neuropsychological function was determined by trained neuropsychologists using official parallel versions of the MoCA. The early MoCA assessments (within 72 hours) were conducted in the intensive care unit, with recent literature indicating that the testing environment (intensive care unit or quiet office) does not influence the test's reliability.[26] HRQOL was evaluated on admission (pre-aSAH) and at 3 months using the EuroQol-5D (EQ-5D) questionnaire. For details regarding the methods of data collection and outcome assessment, we refer to the previously published protocol.[17]

Management of Hydrocephalus

Acute hydrocephalus was defined as ventricular enlargement on CT or MRI studies (bicaudate index above the 95th percentile for age), with or without associated signs such as periventricular edema, in conjunction with an altered/decreased level of consciousness.[11] In case of hydrocephalus on admission, CSF diversion was implemented as an emergency procedure before occlusion therapy of the ruptured aneurysm. In all participating centers, frontal EVD insertion is the first choice, with LDs only considered in alert patients with cleared fourth ventricle and no signs of significant brain edema, extraaxial hematoma, or other supratentorial mass lesion.

Weaning from CSF drainage was usually started in awake patients with aSAH without signs of DCI at approximately day 7, and in comatose patients or those with signs of DCI—depending on drainage quantity—between days 12 and 20 in all centers. Weaning could include gradual increase of the drop chamber but also rapid closure. Given that an earlier trial showed equipoise in terms of shunt-dependent hydrocephalus, this decision was left to the treating physicians' preference.[4] All patients in whom weaning failed received VPS insertion.

Successful weaning was defined as removal of EVD or LD with stable neurological status and without the necessity of VPS insertion. Unsuccessful weaning was defined as VPS insertion at any time point within the 3 months after aSAH.

Data Handling

All data were collected by teams including a local principal investigator and physicians and were entered into a central secure database with audit trail (REDCap) run by the Clinical Trials Center of the University of Zurich. Regular data review for completeness and quality was conducted by the coordinating project leader (M.N.S.).

Statistical Analysis

Depending on normal distribution, we described continuous variables using mean and standard deviation or median with interquartile range (IQR) and categorical variables with frequencies and percentages. In a first step, we compared demographic baseline characteristics in patients with and without successful weaning. We further evaluated the association of these characteristics with our outcome variables of interest (ΔMoCA, which represents the difference in change of achieved MoCA score between < 72 hours and 14–28 days post-aSAH, between 14–28 days and 3 months, and between < 72 hours and 3 months; dichotomized mRS; NIHSS; EQ-5D; and return to home at 3 months) by using univariable linear and logistic regression models. We then constructed multivariable models for the outcome variables of interest. Due to the relatively low number of outcome events, the multivariable model was adjusted for the prespecified variables of age, intraventricular hemorrhage (IVH), and successful versus unsuccessful weaning. A change of 2 points on the MoCA was considered clinically meaningful.[27]

We performed all statistical analyses using Stata software (release 15, StataCorp LLC). The significance level was set at $p = 0.05$.

Ethical Considerations

Institutional review board approval was received from all participating sites under governance by the local ethics committee of Zurich, Switzerland. All patients (or in case of lack of capacity, a relative) provided written informed consent. This study was registered with the ClinicalTrials.gov database (http://clinicaltrials.gov) and its registration no. is NCT03032471. All data can be obtained from the corresponding author upon reasonable request.

Results

Patient Sample

Of the 126 patients recruited, 54 (42.9%) developed hydrocephalus and received CSF diversion. EVD or LD weaning was possible in 37 patients (68.5%) and failed in 17 patients (31.5%), requiring VPS insertion up until 3 months post-aSAH. See Table 1 for baseline characteristics for all patients and for subgroups of patients with successful or unsuccessful weaning.

Patients with unsuccessful weaning were older than those who were successfully weaned (64.5 vs 50.8 years, $p = 0.003$; Table 1). They presented more commonly with ruptured aneurysm in the anterior cerebral artery complex (64.7% vs 35.1%) and had higher rates of IVH (52.9% vs 24.3%, $p = 0.04$). Of note, the modified Fisher and the World Federation of Neurosurgical Societies scores were not associated with study group allocation (all p values > 0.05).

Outcome Analysis

Patients with successful versus unsuccessful weaning had similar MoCA results at 48–72 hours (20.3 vs 20.8, $p = 0.6$) and at 3 months post-aSAH (25.7 vs 23.6, $p = 0.45$; see Fig. 1 for MoCA distribution by weaning and assessed time point). Patients with unsuccessful weaning had significantly worse MoCA results at 14–28 days post-aSAH (15.1 vs 20.6, $p = 0.03$). The median change in MoCA from 48–72 hours to 3 months post-aSAH was 5 (IQR 6) in patients with successful and 0.5 (IQR 6) in patients with unsuccessful weaning. In univariable linear regression, the MoCA score on follow-up for successfully weaned patients was 3 points higher compared to patients who could not be weaned (coefficient 3, 95% CI −1.37 to 7.37, $p = 0.17$). After adjustment for age and IVH, ΔMoCA for successfully weaned patients was significantly better when comparing 14–28 days to baseline (adjusted coefficient 6.80, 95% CI 1.57–12.04, $p = 0.01$), as well as when comparing 3 months to baseline (adjusted coefficient 7.60, 95% CI 3.09–12.11, $p = 0.02$; Table 2).

There were no differences in favorable disability outcome (mRS score 0–3: 93.9% vs 87.5%, $p = 0.45$); neurological status (NIHSS: 0 vs 0, $p = 0.31$); HRQOL outcomes (EQ-5D index: 0.66 vs 0.74, $p = 0.36$); or return-to-home rates at 3 months (75.7% vs 75.0%, $p = 0.28$; Table 2).

Discussion

In this study we set out to explore the differences in the clinical course that patients with aSAH and acute hydrocephalus may have when successfully weaned versus treated for permanent CSF diversion. In our retrospective analysis of a data set derived from the multicenter MoCA-DCI study,[28] several interesting findings emerged. First, we noticed that patients who can successfully be weaned show a marked and clinically meaningful improvement in neuropsychological function over time, which is not evident in those in whom weaning fails. Second, the different dynamics in neuropsychological improvement happened between 48–72 hours and 14–28 days, in which the successfully weaned patients had a steeper recovery. However, we saw resolution of the difference between successfully and unsuccessfully weaned patients at 3 months, which might be due to the positive effects of permanent CSF diversion. Third, the differences in outcome between

TABLE 1. Baseline characteristics in 126 patients with hydrocephalus after aSAH

	Overall Cohort, n = 126	Successful Weaning, n = 37	Unsuccessful Weaning, n = 17	p Value
Age in yrs, mean (SD)	53.9 (13.5)	50.8 (12.4)	64.5 (13.1)	**0.003**
Sex, no. (%)				0.20
Male	44 (34.9)	13 (35.1)	3 (17.6)	
Female	82 (65.1)	24 (64.9)	14 (82.4)	
Arterial hypertension, no. (%)	39 (31.0)	12 (32.4)	8 (47.1)	0.30
Smoking, no. (%)	116 (92.1)	34 (91.9)	15 (88.2)	**0.05**
Never	47 (40.5)	16 (47.1)	7 (46.7)	
Former	13 (11.2)	2 (5.9)	5 (33.3)	
Active	56 (48.3)	16 (47.1)	3 (20.0)	
Admission data				
Aneurysm location, no. (%)				0.14
ACA complex	58 (46.0)	13 (35.1)	11 (64.7)	
MCA complex	30 (23.8)	10 (27.0)	4 (23.5)	
ICA complex	31 (24.6)	11 (29.7)	1 (5.9)	
Posterior circulation	7 (5.6)	3 (8.1)	1 (5.9)	
Aneurysm diam in mm, median (IQR)	5.4 (4)	6 (4.7)	5 (1.75)	0.13
IVH, no. (%)	27 (21.4)	9 (24.3)	9 (52.9)	**0.04**
ICH, no. (%)	10 (7.9)	4 (10.8)	1 (5.9)	0.57
Multiple aneurysms, no. (%)	27 (21.4)	6 (16.2)	4 (23.5)	0.52
Modified Fisher Scale score, no. (%)				0.37
1	32 (25.4)	5 (13.5)	2 (11.8)	
2	7 (5.6)	2 (5.4)	3 (17.6)	
3	72 (57.1)	23 (62.2)	7 (41.2)	
4	13 (10.3)	7 (18.9)	5 (29.4)	
WFNS score, no. (%)				0.69
1–3	118 (93.7)	32 (86.5)	14 (82.4)	
4–5	8 (6.3)	5 (13.5)	3 (17.6)	
Aneurysm occlusion, no. (%)				
Microsurgical clipping*	42 (33.3)	13 (35.1)	4 (23.5)	0.40
Endovascular coiling†	84 (66.7)	24 (64.9)	13 (76.5)	0.11
Complications, no. (%)				
Epileptic seizure	8 (6.4)	3 (8.1)	1 (5.9)	0.77
DCI	31 (24.6)	15 (40.5)	5 (29.4)	0.43
Cerebral infarct	14 (11.1)	8 (21.6)	2 (11.8)	0.39
Aneurysm rebleeding	3 (2.4)	3 (8.1)	0	
Ventriculitis	4 (3.2)	2 (5.4)	2 (11.8)	0.42
Death	1 (0.8)	1 (2.7)	0	

ACA = anterior cerebral artery; diam = diameter; ICA = internal carotid artery; ICH = intracerebral hemorrhage; MCA = middle cerebral artery; WFNS = World Federation of Neurosurgical Societies.
Boldface type indicates statistical significance.
* The treatment may include trapping, wrapping, or bypass surgery, if required.
† The treatment may include insertion of stents or flow diverters, if required.

both groups were subtle and were not evident on other commonly used outcome scales like the mRS, NIHSS, EQ-5D index, or time of return to home.[29] It is important to highlight that our analysis method is hypothesis generating and cannot demonstrate actual causality.

It has been known for decades that aSAH may lead to neuropsychological deficits,[30] and these patients have received more attention in recent years.[23,24,28] Hydrocephalus was identified as a predictor for poor cognitive function in the acute phase (as was DCI), due to an increase of intracranial pressure and diffuse brain damage causing white matter abnormalities, among other reasons.[31–34] CSF diversion after aSAH has been shown to be associated with significant improvement in outcome.[5,35] Many studies

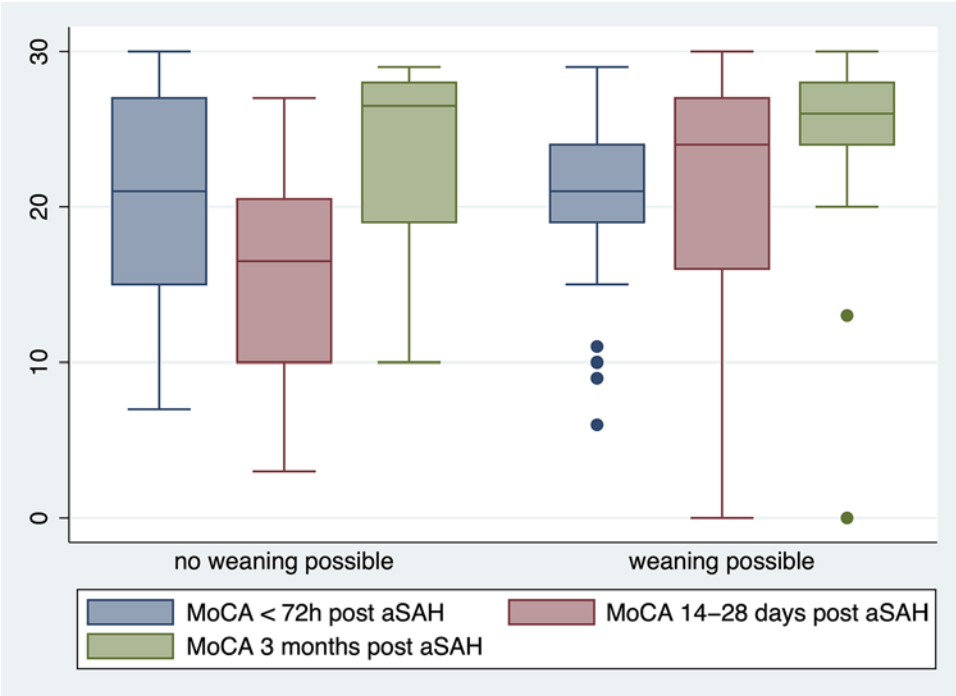

FIG. 1. Box plot showing distribution of MoCA scores by successful versus unsuccessful weaning and time point of measurement. *Circles* represent data outliers.

in recent years have focused on prediction of functional outcome as well as its potential modifiers.[12,13,36–41] Only a few studies conducted subgroup analyses in patients with aSAH and hydrocephalus to evaluate CSF diversion and successful versus unsuccessful weaning. However, those did mostly focus on timing or management of weaning and consecutive shunt dependency.[42–44] There are still only limited data on the influence of hydrocephalus, as well as on success versus failure of weaning on the neuropsychological outcome in these patients. This was the focus of our analysis.

In this study, participants were evaluated clinically and neuropsychologically during their stay according to our prepublished protocol and were followed up after 3 months.[17] Patients with successful weaning had a better MoCA score both at 14–28 days and at 3-month follow-up, compared to their baseline measurements. However, we did not find a difference in MoCA when comparing the scores

TABLE 2. Univariable and adjusted analysis of outcomes of successfully and unsuccessfully weaned patients with aSAH

	Weaning Status*		Univariable Analysis		Adjusted for Age & IVH on Admission	
	Successful, n = 37	Unsuccessful, n = 17	Coefficient/OR (95% CI)	p Value	Coefficient/OR (95% CI)	p Value
ΔMoCA 48–72 hrs vs 14–28 days, median	2 (IQR 4)	−4 (IQR 9.5)	5.86 (1.34 to 10.37)	**0.01**	6.80 (1.57 to 12.04)	**0.01**
ΔMoCA 48–72 hrs vs 3 mos, median	5 (IQR 6)	0.5 (IQR 6)	3 (−1.37 to 7.37)	0.17	7.60 (3.09 to 12.11)	**0.02**
ΔMoCA 14–28 days vs 3 mos, median	3 (IQR 8)	6 (IQR 12)	−3.04 (−7.94 to 1.87)	0.22	1.20 (−4.13 to 6.54)	0.65
mRS score at 3 mos			2.21 (0.28 to 17.36)	0.45	1.48 (0.22 to 10.07)	0.69
0–3	31 (93.9%)	14 (87.5%)				
4–6	2 (6.1%)	2 (12.5%)				
NIHSS score at 3 mos, median	0 (IQR 0)	0 (IQR 1)	−0.63 (−1.86 to 0.61)	0.31	−0.48 (−1.91 to 0.95)	0.5
EQ-5D index at 3 mos, median	0.66 (IQR 0.23)	0.74 (IQR 0.28)	−0.06 (−0.20 to 0.08)	0.36	−0.12 (−0.28 to 0.05)	0.16
Return home at 3 mos	28 (75.7%)	12 (75.0%)†	2.3 (0.50 to 10.91)	0.28	2.05 (0.31 to 13.56)	0.46

Δ = change.
Main outcome assessment was at 3 months; an additional time point of assessment was at 14–28 days post-aSAH. Boldface type indicates statistical significance.
* Unless otherwise indicated, values represent the number of patients (%).
† In 1 patient this status was unknown, so the percent was calculated for 12/16.

at time of discharge (14–28 days) and 3 months. The different neuropsychological outcome profiles, as evident from Table 2, have several implications for clinical patient care. Interestingly, the rate of CSF diversion was lower in our cohort compared to what has been previously described. The most likely reason is that we only included alert patients with aSAH in order to evaluate the MoCA score.

First, critically analyzing the change in neuropsychological function over time, it appears that in our cohort the differentiation between patients who could be weaned and those who needed a permanent shunt was reasonably good. Table 2 illustrates that patients who regain the ability for physiological CSF production and resorption are likely to improve on the MoCA by 2 points on average during the hospitalization—the threshold of what is considered clinically meaningful.[27] On the contrary, those who do not regain this ability deteriorate by 4 points on the MoCA on average during the same time period. The MoCA could hence be used as a screening tool for alert patients with aSAH on the ward,[24] to make sure that subtle worsening—potentially due to the development of chronic hydrocephalus—is not missed. Our findings suggest that in patients in whom the EVD or LD has been removed, but who show no cognitive improvement over the course of 1–2 weeks, a repeat CT scan might be considered to rule out chronic hydrocephalus. Whether this would indeed uncover patients with untreated, chronic hydrocephalus merits evaluation in a future, prospective study.

Moreover, we show that once a permanent CSF diversion device is installed, patients improve dramatically—on average 6 points on the MoCA—between 14–28 days and 3 months post-aSAH. They seem to catch up from the delay in neuropsychological recovery compared to the group with successful CSF diversion, to the extent that at 3 months there are no gross differences on any recommended outcome scale—including neuropsychological function, disability, neurological status, and HRQOL. Our findings are consistent with previous literature.[12,45] There are several possible reasons why we found no significant between-group difference for the time point 14–28 days to 3 months: 1) there really might be no difference; 2) the MoCA—as the recommended screening instrument for patients with aSAH—may not be sensitive enough to detect small differences; and 3) due to the limited sample size, the study might be underpowered to detect a small difference.[25,46]

Strengths and Limitations

The main strength of this study is its design, providing valuable longitudinal detailed outcome parameters—including neuropsychological function—in a multicenter setting, which includes patients from all cultural and linguistic areas of Switzerland. This, together with the small but existing inevitable differences in patient management between participating centers, improves the generalizability of the current findings to other settings. Finally, the observed results are in line with our clinical experience, which lends credibility to the data and conclusions.

However, the total cohort of patients with availability of the required variables was limited to 54 patients. This may have resulted in insufficient power of the study to detect further, smaller effects. The included sample was limited to patients with good-grade aSAH, due to the inclusion criteria of a Glasgow Coma Scale score ≥ 13 points (i.e., alert patients), which introduces bias but was inevitable, given that patients with higher-grade aSAH cannot be neuropsychologically tested in the acute setting due to their decreased consciousness level. In addition, cognitive rehabilitation continues after 3 months, but this study did not foresee a longer-term follow-up. In consequence, we are unable to detect a difference that might appear after 3 months. Using the MoCA—as a recommended and feasible screening tool[25,26,28]—for the neuropsychological evaluation was a pragmatic decision, but its sensitivity for the detection of cognitive deficits is lower compared to the Neurological Assessment Battery or other specialized testing batteries.[23,25,26,28,47]

Conclusions

Our results demonstrate that patients who succeed in restoration of physiological CSF dynamics improve on average by 2 points on the MoCA between 48–72 hours and 14–28 days, whereas those in whom weaning fails worsen by 4 points. Patients who receive permanent CSF diversion (i.e., a VPS) show significant neuropsychological improvement thereafter, catching up from the delay in neuropsychological improvement until 3 months post-aSAH; 3 months post-aSAH, patients with successful weaning and those with permanent CSF diversion fare equally well in terms of neuropsychological, neurological, disability, and HRQOL outcomes. This underlines the importance of treating chronic hydrocephalus in patients with aSAH, given that it significantly influences their cognitive outcome and consequently functional capability and independence. Patients who do not show progressive neuropsychological improvement after weaning should be considered for repeat CT imaging to rule out chronic (untreated) hydrocephalus.

Appendix

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Disclosures

Dr. Regli reported grants from Actelion Pharmaceuticals, Ltd., during the conduct of the study; he also reported grants from Stryker and personal fees from B Braun outside the submitted work. Dr. Stienen reported grants from Idorsia Pharmaceuticals, Ltd.: a research grant was paid to his institution during the conduct of the study.

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Supplemental Information

Videos

Video Abstract. https://vimeo.com/805949004.

Previous Presentations

Presented at the European Association of Neurosurgical Societies (EANS) 2022 meeting, held in Belgrade, Serbia, October 16–20, 2022.

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