



# Predicting factors for shunt-dependent hydrocephalus in patients with aneurysmal subarachnoid hemorrhage

Yung Ki Park<sup>1</sup> · Hyeong-Joong Yi<sup>1</sup> · Kyu-Sun Choi<sup>1</sup> · Young-Jun Lee<sup>2</sup> · Hyoung-Joon Chun<sup>1</sup> · Sae Min Kwon<sup>1</sup> · Dong-Won Kim<sup>3</sup>

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## Abstract

**Background** Chronic hydrocephalus after aneurysmal subarachnoid hemorrhage (SAH) is a major complication that leads to a medical burden and poor clinical outcomes. The aim of this study was to evaluate the predictive factors of shunt-dependent hydrocephalus focusing on postoperative fever and infection.

**Method** A total of 418 patients were included in this study and the patient demographic features, radiologic findings, days of fever burden, and infection were compared between the shunt ( $n = 72$ ) and no shunt group ( $n = 346$ ). Days of fever burden was defined as the total number of days with the highest body temperature  $\geq 38.0$  °C each day from day 1 to day 14. Pneumonia, urinary tract infection (UTI), meningitis, and bacteremia were recorded in all patients.

**Results** The independent predictive factors for shunt-dependent hydrocephalus were older age  $\geq 65$ , microsurgical clipping, placement of extraventricular drainage (EVD), days of fever burden, and infection. The incidence of shunt dependency was 2.4% in the no fever burden patients ( $n = 123$ ), 14.9% in the 1–3 days of fever burden patients ( $n = 161$ ), 27.0% in the 4–6 days of fever burden patients ( $n = 74$ ), and 41.7% in the  $\geq 7$  days of fever burden patients with statistical significance among groups ( $p < 0.001$ ).

**Conclusion** The rate of shunt dependency increased proportionally as the days of fever burden increased. Older age ( $\geq 65$ ), microsurgical clipping, placement of EVD, days of fever burden, and infection were independent predictive factors for shunt dependency. Proper postoperative care for maintaining normal body temperature and preventing infectious disease can help reduce the rate of shunt dependency and improve clinical outcomes.

**Keywords** Hydrocephalus · Aneurysmal subarachnoid hemorrhage · Fever · Infection

## Introduction

Despite improvements in management, aneurysmal subarachnoid hemorrhage (SAH) is a devastating disease with a high morbidity. Patients who survive this disease suffer from

complications such as seizures, cognitive impairment, delayed cerebral ischemia, and chronic hydrocephalus. According to previous studies, shunt-dependent hydrocephalus after aneurysmal SAH occurs in 6–67% of patients [7, 10, 29, 32].

Hydrocephalus is a condition of cerebral ventricle enlargement with cerebrospinal fluid (CSF) accumulation. Failure of homeostasis in CSF production and reabsorption are the main features of this disease. The mechanism of hydrocephalus varies and includes obstruction of ventricles due to blood production, malabsorption of CSF due to fibrosis or inflammation of arachnoid villi, and loss of ventricle compliance [2–5, 16, 21]. Recently, inflammation-dependent CSF hypersecretion by the choroid plexus epithelium has been reported in an animal model [22].

Previous studies reported that intraventricular hemorrhage (IVH), hypertension, initial acute hydrocephalus, extraventricular drainage (EVD), poor Hunt and Hess, and higher Fisher grade, symptomatic vasospasm, female sex, and meningitis were the

✉ Hyeong-Joong Yi  
hjyi8499@hanyang.ac.kr

<sup>1</sup> Department of Neurosurgery, Hanyang University Medical Center, Seoul, South Korea

<sup>2</sup> Department of Radiology, Hanyang University Medical Center, Seoul, South Korea

<sup>3</sup> Department of Anesthesiology and Pain Medicine, Hanyang University Medical Center, Seoul, South Korea

predicting factors for shunt-dependent hydrocephalus [1, 7, 10, 13, 18, 20, 24, 27, 29, 31, 34, 35]. Chronic hydrocephalus leads to not only cognitive impairment but also a higher medical burden due to the need for additional surgeries and high rates of failure and infection.

Postoperative fever is relatively common in SAH patients compared to other brain pathologies. Since inflammation is involved in the development of hydrocephalus, it may be useful to investigate the relationship between postoperative fever and shunt-dependent hydrocephalus. We were also curious if infection is related to shunt dependency. The aim of this study was to evaluate the predicting factors of shunt-dependent hydrocephalus after aneurysmal SAH, focusing on postoperative fever and infection.

## Methods and materials

We retrospectively reviewed the medical records of aneurysmal SAH patients who visited our institution between January 2007 and December 2016. The inclusion criteria were as follows: (1) both sexes within 18–85 years old, (2) identification of a ruptured aneurysm in a radiologic study such as computed tomography (CT) or cerebral angiography, and (3) aneurysm obliteration performed with either a clip or coil within 72 h after SAH ictus. Exclusion criteria consisted of therapeutic hypothermia, death before 14 days after SAH ictus, previous stroke or neurologic deficits, mental retardation, psychological disease, and loss of follow-up before 6 months. This study was approved by the institutional review board at the author's institute (HYUH IRB 2017-10-008-001).

Among the 548 patients who were treated for aneurysmal SAH at our institution, 418 patients satisfied the inclusion criteria and were included in the study. The patients who received a shunt operation with either a ventriculoperitoneal or lumboperitoneal shunt were categorized as the shunt group, and the rest of the patients were categorized as the no shunt group.

Patients were treated with either microsurgical clip ligation or endovascular coil embolization with or without stent assistance. EVD was performed in patients with ventricle enlargement or bleeding in the ventricles causing mental deterioration. Weaning of EVD was first attempted usually 3 to 5 days after insertion. The height of the dripping chamber was usually positioned 10 cm above the tragus level and was gradually increased to 20 cm above the tragus. In patients who did not show mental deterioration after a gradual increase of the chamber, the EVD was clamped and a CT scan was performed after 24 h to evaluate the ventricular enlargement. The EVD was removed in patients who showed a tolerable ventricle size at follow-up CT scan without mental deterioration. In patients who showed persistent elevation of ICP or failed the weaning trial, EVD was maintained until 7 days after insertion.

Additional EVD at different sites or lumbar drainage was performed for patients who needed CSF drainage for longer than 7 days to prevent CSF infection. Shunt operations were performed for patients who continued to show ventricle enlargement after 14 days correlating with symptoms such as mental deterioration, cognitive impairment, and incontinence. Patients who failed the weaning trials of the EVD were also considered for a shunt operation.

Demographic features were reviewed based on the previous medical records. Sex, age, Hunt and Hess grade [19], hypertension (HTN), diabetes mellitus (DM), and body mass index (BMI) were included. The Hunt and Hess grade was categorized as either good (I–II) or poor (III–V). Radiologic findings included the modified Fisher scale, initial acute hydrocephalus, bicaudate index, IVH, concomitant intracerebral hemorrhage (ICH), SAH sum score, and IVH sum score. Acute hydrocephalus was defined as higher than the upper normal 95 percentile matched by age using the bicaudate index (<36 years, 0.16; 36–45 years, 0.17; 46–55 years, 0.18; 56–65 years, 0.19; 66–75 years, 0.20; 76–85 years, 0.21) [15]. The SAH sum score (0 to 30) was calculated by the means of the Hijdra score by adding the amount of blood in ten cistern or fissure points (0 to 3 each) [17]. The IVH sum score (0 to 12) was calculated by the means of the Graeb score by adding the score of each ventricle (lateral ventricle, 0–4; third ventricle, 0–2; fourth ventricle, 0–2) [12]. Radiologic findings were recorded by a single neuro-radiologist (Y-J. Lee) in a blind fashion. Delayed cerebral ischemia (DCI) was defined as the occurrence of focal neurological impairment or a decrease of at least two points on the Glasgow coma scale score or on one of its individual components lasting at least 1 h that cannot be attributed to other causes [33].

Body temperature between day 1 and day 14 was recorded in all patients. Day 0 was defined as the day of SAH ictus. Days of fever burden were defined as the total number of days with the highest body temperature  $\geq 38.0$  °C each day from day 1 to day 14. Furthermore, patients were categorized into an early fever group and a late fever group to analyze the impact of fever according to the fever period. The early fever group was defined as two or more days of the highest body temperature  $\geq 38.0$  °C from day 1 to day 7. The late fever group was defined as two or more days of the highest body temperature  $\geq 38.0$  °C from day 8 to day 14. Axillary body temperature was measured every hour in the neurointensive care unit and every 4 to 6 h in the general ward. In patients with fever, antipyretic drugs such as acetaminophen and non-steroid anti-inflammatory drugs (NSAIDs) and a cool blanket were applied to maintain a normal temperature. Chest X-rays, urine testing, and routine culture (tracheal or sputum, urinary, and blood) were performed for the fever patients. CSF cell count and culture were performed for patients who were suspicious for meningitis. Pneumonia was defined as a new focal infiltrate in the lung field plus more than two of the following

criteria: (1) temperature  $> 38.0$  °C; (2) leukocytosis  $> 10,000$  cells/mm<sup>3</sup>; and (3) purulent respiratory secretion [26]. Urinary tract infection (UTI) was defined as a positive urine culture with pyuria. Meningitis was defined as a positive CSF culture with a fever  $\geq 38.0$  °C. Bacteremia was defined as a positive blood culture with a fever  $\geq 38.0$  °C.

Nonparametric variables were compared using the chi-square and Fisher exact test. Parametric variables with a normal distribution were compared by the independent *t* test and without a normal distribution by the Mann-Whitney *U* test. Data are presented as the mean ( $\pm$  standard deviation) for continuous variables with a normal distribution, median [interquartile range (IQR)] for continuous variables without a normal distribution, and frequency (percentage) for categorical variables. Variables with a value of  $p < 0.10$  were reentered in the multivariate logistic regression model with a backward stepwise method. The odds ratio and 95% confidence index (CI) were presented for statistically significant factors ( $p < 0.05$ ). All of the recorded data were analyzed with R version 3.3.2 (<https://www.r-project.org/>; R Foundation for Statistical Computing, Vienna, Austria).

## Results

Among 418 aneurysmal SAH patients, 72 (17.2%) patients underwent a CSF diversion shunt operation due to chronic hydrocephalus. Table 1 shows the summary of the total aneurysmal SAH patients who were enrolled in the study. A comparison of demographic features and radiologic findings between the shunt and no shunt group is demonstrated in Table 2. Older age, microsurgical clipping, poor Hunt and Hess grade (III–V), initial acute hydrocephalus, EVD, presence of IVH and ICH, larger amount of SAH and IVH, occurrence of DCI, days of fever burden, and infection showed significant differences ( $p < 0.05$ ) between the shunt group and no shunt group. Median days of fever were higher in the shunt group compared with the no shunt group (5 versus 2 days,  $p < 0.001$ ). Among the co-factors of infection, pneumonia was diagnosed more frequently in the shunt group (30.6%) compared to the no shunt group (10.8%).

Logistic regression analysis of shunt-dependent hydrocephalus is demonstrated in Table 3. Five variables remained statistically significant after adjusting for confounding factors: (1) older age  $\geq 65$  (OR 2.96, 95% CI = 1.64–5.35,  $p = 0.0003$ ), (2) microsurgical clipping (OR 2.37, 95% CI = 1.19–5.07,  $p = 0.0186$ ), (3) placement of EVD (OR 3.33, 95% CI = 1.55–7.09,  $p = 0.0018$ ), (4) days of fever burden (OR 1.21, 95% CI = 1.11–1.32,  $p < 0.0001$ ), and (5) infection (OR 1.83, 95% CI 1.00–3.34,  $p = 0.0486$ ).

The percentage of shunt-dependent chronic hydrocephalus cases according to days of fever burden is displayed in Fig. 1. Patients with no days of fever burden had a shunt dependency

**Table 1** Summary of total aneurysmal subarachnoid hemorrhage patients

Sex (%)	
Female	283 (67.7)
Male	135 (32.3)
Age	55.0 [47.0; 64.0]
Treatment modality (%)	
Clip	295 (70.6)
Coil	123 (29.4)
Hunt and Hess grade (%)	
I	37 (8.9)
II	177 (42.3)
III	121 (28.9)
IV	79 (18.9)
V	4 (1.0)
Modified Fisher scale (%)	
1	49 (11.7)
2	7 (1.7)
3	138 (33.0)
4	224 (53.6)
Initial acute hydrocephalus (%)	123 (29.4)
IVH (%)	231 (55.3)
Concomitant ICH (%)	117 (28.0)
Shunt operation (%)	72 (17.2)
Delayed cerebral ischemia (%)	62 (14.8)
Infection (%)	109 (26.2)
Pneumonia	59 (14.2)
Urinary tract infection	34 (8.2)
Meningitis	7 (1.7)
Bacteremia	20 (5.4)

IVH intraventricular hemorrhage; ICH intracerebral hemorrhage

rate of 2.4%; 1–3 days of fever burden, 14.9%; 4–6 days, 27.0%; and more than 7 days, 41.7%, the differences of which were statistically significant ( $p < 0.001$ ).

Shunt dependency rates of the early fever group (two or more days of the highest body temperature  $\geq 38.0$  °C from day 1 to day 7) was 29.2% (38/130) and the late fever group (two or more days of highest body temperature  $\geq 38.0$  °C from day 8 to day 14) was 30.2% (52/172) without statistical significance ( $p = 0.951$ ).

## Discussion

The overall rate of shunt-dependent chronic hydrocephalus in the current study was 17.7%, which is consistent with the literature [10, 28, 29, 31, 35, 37]. Chronic hydrocephalus leads to loss of cognitive and memory function, worse clinical outcomes, and prolonged length of stay in the hospital [27]. The shunt operation itself carries a high risk of reoperation due to malfunction and

**Table 2** Comparison of demographic features and radiologic findings between the shunt and no shunt group

	No shunt ( <i>N</i> = 346)	Shunt ( <i>N</i> = 72)	<i>p</i> value
Female sex	230 (66.5%)	53 (73.6%)	0.298
Age	53.5 [46.0; 62.0]	61.5 [54.0; 69.0]	< 0.001
Old age			< 0.001
< 65 (%)	274 (79.2)	41 (56.9)	
≥ 65 (%)	72 (20.8)	31 (43.1)	
Operation type			0.029
Clip (%)	236 (68.2)	59 (81.9)	
Coil (%)	110 (31.8)	13 (18.1)	
Circulation			0.475
Anterior (%)	315 (91.0)	68 (94.4)	
Posterior (%)	31 (9.0)	4 (5.6)	
Hunt and Hess grade			< 0.001
Good grade (I–II) (%)	193 (55.8)	21 (29.2)	
Poor grade (III–V) (%)	153 (44.2)	51 (70.8)	
Modified Fisher scale			0.031
1 (%)	43 (12.4)	6 (8.3)	
2 (%)	6 (1.7)	1 (1.4)	
3 (%)	123 (35.5)	15 (20.8)	
4 (%)	174 (50.3)	50 (69.4)	
Initial acute hydrocephalus	94 (27.2%)	29 (40.3%)	0.038
EVD	23 (6.6%)	18 (25.0%)	< 0.001
IVH	180 (52.0%)	51 (70.8%)	0.005
Bicaudate index	16.4 [14.2; 19.1]	18.1 [15.2; 21.4]	0.003
SAH sum score	18.0 [10.0; 26.0]	25.0 [14.0; 28.0]	0.002
IVH sum score	1.0 [0.0; 2.0]	2.0 [1.0; 6.0]	< 0.001
Concomitant ICH	85 (24.6%)	32 (44.4%)	0.001
Delayed cerebral ischemia	44 (12.7%)	18 (25.0%)	0.013
Hypertension	124 (35.8%)	31 (43.1%)	0.308
Diabetes mellitus	25 (7.2%)	4 (5.6%)	0.801
Days of fever burden	2.0 [0.0; 4.0]	5.0 [2.0; 7.0]	< 0.001
Infection	75 (21.8%)	34 (47.2%)	< 0.001
Pneumonia	37 (10.8%)	22 (30.6%)	< 0.001
Urinary tract infection	25 (7.3%)	9 (12.5%)	0.216
Meningitis	4 (1.2%)	3 (4.2%)	0.194
Bacteremia	14 (4.6%)	6 (8.8%)	0.270

*EVD* extraventricular drainage; *IVH* intraventricular hemorrhage; *SAH* subarachnoid hemorrhage; *ICH* intracerebral hemorrhage

infection. Additionally, the most common reason for readmission after aneurysmal SAH is hydrocephalus [14].

Older age (over 65) was an independent predicting factor for shunt dependency, which is consistent with the literature. Brain atrophy enlarges the ventricle size and allows for more ventricular blood flow in SAH patients. Fibrosis of the meningeal and arachnoid membranes leads to impairments in CSF circulation and a decrease in CSF absorption [39]. The lower compliance of the ventricles and longer CSF circulation time make older patients more vulnerable to chronic hydrocephalus [25].

Microsurgical clipping was an independent predicting factor for shunt dependency in the current study. There are a few potential mechanisms that may explain its effect on disturbances of CSF circulation during surgical clipping of a ruptured aneurysm. Several studies have emphasized the function of CSF absorption in the subcortical microcirculation [3, 9, 18]. Brain retraction and manipulation of small vessels during surgical clipping can disrupt the absorption of CSF by small vessels. Minimizing brain retraction and the manipulation of blood vessels may be helpful not only in reducing brain parenchyma injury but also in maintaining CSF homeostasis.

**Table 3** Logistic regression analysis of shunt-dependent hydrocephalus

	Univariate			Multivariate		
	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value
Old age ( $\geq 65$ )	2.88	1.68–4.90	0.0001	2.96	1.64–5.35	0.0003
Clip	2.12	1.15–4.18	0.0221	2.37	1.19–5.07	0.0186
Hunt and Hess grade	3.06	1.79–5.41	0.0001			
Modified Fisher scale	1.42	1.05–1.99	0.0302			
EVD	4.68	2.35–9.24	<0.0001	3.33	1.55–7.09	0.0018
Initial acute hydrocephalus	1.42	1.05–1.99	0.0277			
IVH	2.24	1.31–3.95	0.0041			
Concomitant ICH	2.46	1.45–4.15	0.0008			
Bicaudate index	1.12	1.05–1.19	0.0006			
SAH sum score	1.04	1.01–1.07	0.0088			
IVH sum score	1.19	1.10–1.29	<0.0001			
Delayed cerebral ischemia	2.29	1.21–4.21	0.0089			
Days of fever burden	1.27	1.17–1.38	<0.0001	1.21	1.11–1.32	<0.0001
Infection	3.21	1.89–5.45	<0.0001	1.83	1.00–3.34	0.0486

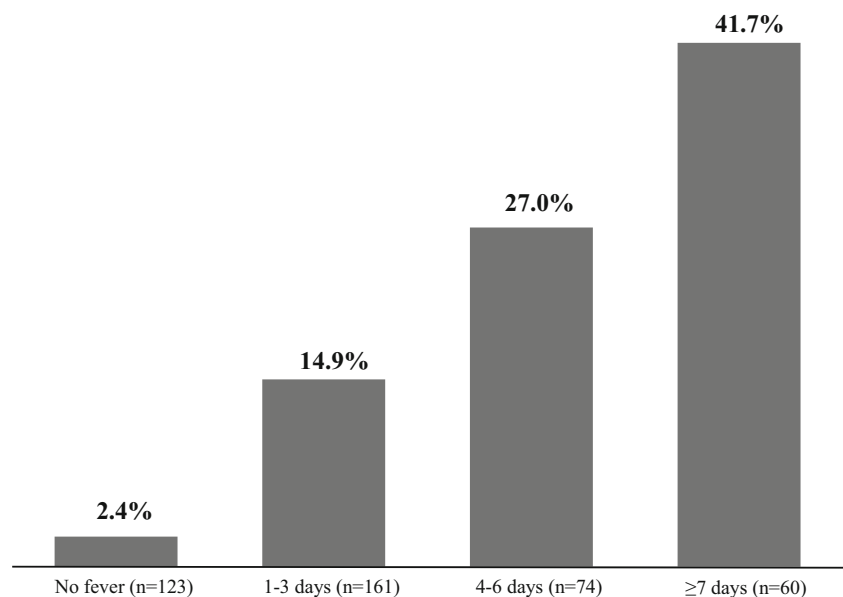
OR odds ratio; CI confidence index; EVD extraventricular drainage; IVH intraventricular hemorrhage; ICH intracerebral hemorrhage; SAH subarachnoid hemorrhage

However, the relationship between surgical method, either clip or coil, and shunt dependency has not yet been clarified. De Oliveira et al. showed that clipping may be associated with a lower risk of shunt dependency [8]. Additionally, a meta-analysis showed that endovascular coiling has a trend towards shunt dependency compared to surgical clipping.

In the current study, placement of EVD and acute hydrocephalus at the initial CT scan were associated with shunt dependency in the univariate analysis, which is consistent with the literature. The bicaudate index and amount of SAH and IVH were also associated with shunt dependency in the

univariate analysis, but only EVD showed statistical significance in the multivariate analysis. Acute stage hydrocephalus after SAH is usually caused by obstruction or adhesion of ventricles due to blood production in the ventricles and subarachnoid space. Interfering arachnoid villi were thought to be the main mechanism for shunt dependency, but a recent study showed that overproduction of CSF after bleeding could also contribute to chronic hydrocephalus [22]. The mechanism of progression from acute to chronic hydrocephalus is still not well understood and further studies should be performed to clarify this problem.

**Fig. 1** Rate of shunt-dependent hydrocephalus according to days of fever burden between day 1 and day 14 after aneurysmal subarachnoid hemorrhage



The rate of shunt dependency increased proportionally with increasing days of fever burden. Patients with over 7 days of fever burden had a shunt dependency rate of 41.7%. Yang et al. presented a similar result for the relation between fever and shunt dependency, but fever frequency was only evaluated for 7 days with a small group of patients [38]. Fever is one component of systemic inflammation that is triggered by blood production in the subarachnoid space. Several studies have shown that inflammatory markers such as transforming growth factor  $\alpha/\beta$ , interleukin-6, and C-reactive protein are elevated in the CSF and peripheral blood in post-SAH chronic hydrocephalus patients [11, 23, 30, 36]. A higher fever burden can reflect the persistence of systemic inflammation, which seems to be involved in arachnoid granulation and hypersecretion of CSF [22]. Upregulation of inflammatory responses seems to be responsible for shunt dependency following SAH.

We hypothesized that early fever will be more related to severe SAH and IVH and that late fever will be more prone to nosocomial infection. The shunt dependency rate was similar between the early (29.2%) and late fever groups (30.2%) in the current study. Therefore, this indicates that the inflammatory state alone influences the imbalance of CSF circulation, either caused by hemorrhage or nosocomial infection.

Infection was an independent predictor of shunt dependency in the current study. Pneumonia was the only infectious cofactor that was associated with shunt dependency in the univariate analysis ( $p < 0.001$ ). Pneumonia is known to be the most common hospital-acquired complication after SAH and is related to the severity of patients [6]. Postoperative infection is a serious complication, especially in patients who are in a bedridden state. Proper management of fever and infectious disease in the postoperative period may be helpful in preventing shunt operations and thus improving clinical outcomes.

This study contains a few limitations due to its nature as a retrospective study. Treatment modality of either clip or coil was determined by the individual institution and can differ between different institutions. Body temperature was not recorded in a uniform fashion. For patients in the neurointensive care unit, body temperature was checked every hour; however, body temperature was recorded every 4 to 6 h in general ward patients. Measurement of body temperature was estimated by using surface axillary temperature, which is less reliable than deep body temperature, such as in the bladder. The infection rate may be underestimated because laboratory and culture tests were performed only in patients who were suspicious for a particular infection.

## Conclusions

The independent predicting factors for shunt-dependent chronic hydrocephalus after aneurysmal SAH were older age ( $\geq 65$ ), microsurgical clipping, placement of EVD, days of

fever burden, and infection. The rate of shunt dependency increased proportionally as the days of fever burden increased. Proper management of postoperative fever and infection control may lower the rate of shunt dependency and improve clinical outcomes.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the institutional review board at the author's institute (HYUH IRB 2017-10-008-001).

**Informed consent** For this type of study, formal consent is not required.

**Comments** In this study, Park et al. investigate the association between fever and infection during the admission period following aneurysmal SAH and shunt-dependent hydrocephalus. Fever is an unspecific symptom in these severely ill patients and can be caused by infection, a general inflammatory response or a direct effect of the SAH/IVH on the brain parenchyma (hypothalamus). But, as a recent publication in Nature Medicine [22] indicates that intraventricular hemorrhage can cause hypersecretion of CSF (in mice), indicating that hydrocephalus might (at least in part) be related to inflammatory reactions in the choroid plexus. In this retrospective study of 418 patients, the authors correct their analysis for known predictors of shunt dependency and find an independent effect of fever burden on the prevalence of shunt treatment, which could indicate an effect of an inflammatory state on CSF circulation in humans. As mentioned, fever is an unspecific sign and research in risk stratification regarding chronic hydrocephalus following aneurysmal SAH is still needed.

Alexander Lilja-Cyron  
Copenhagen, Denmark

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