Neurosurgical Review (2019) 42:481–488
https://doi.org/10.1007/s10143-018-0990-9

ORIGINAL ARTICLE

Rate and risk factors for a hyperactivity delirium in patients with aneurysmal subarachnoid haemorrhage

Thomas Sauvigny[1] · Malte Mohme[1] · Jörn Grensemann[2] · Lasse Dührsen[1] · Jan Regelsberger[1] · Stefan Kluge[2] · Nils Ole Schmidt[1] · Manfred Westphal[1] · Patrick Czorlich[1]

Received: 18 April 2018 / Revised: 21 May 2018 / Accepted: 30 May 2018 / Published online: 9 June 2018

Abstract

Hyperactive delirium (agitation) is a common complication in patients on intensive care units and can be assessed by the Richmond Agitation and Sedation Scale (RASS) in principle. However, the role of agitation in patients with aneurysmal subarachnoid haemorrhage (SAH) is poorly understood. We performed a retrospective analysis to identify risk factors for the development of a hyperactive delirium and its functional consequences for neurological outcome. Three hundred thirty-eight patients with SAH were screened in this study resulting in 212 patients which reached at least once a RASS of 0 and were eligible for further analysis. Clinical characteristics were analysed towards the occurrence of a hyperactive delirium. Neurological outcome at discharge and follow-up was assessed using the Glasgow Outcome Scale. Seventy-eight of 212 patients (36.8%) developed a hyperactive delirium; the duration ranged from 1 to 11 days. Multivariate regression revealed initial hydrocephalus (odds ratio (OR) 3.21 95% confidence interval (CI) [1.33–7.70]; $p = 0.01$), microsurgical clipping (OR 3.70 95%CI 1.71–8.01]; $p = 0.001$), male gender (OR 1.97 95%CI [1.05–3.85]; $p = 0.047$) and a higher Graeb score (OR 1.11 95%CI [1.00–1.22]; $p = 0.043$) to be significantly associated with the development of agitation. Medical history of psychiatric disorders, alcohol or nicotine abuse showed no correlation with agitation. Cox regression analysis revealed no significant influence of agitation towards unfavourable outcome at discharge or follow-up. We provide four independent risk factors for the development of agitation in SAH patients. Our study emphasizes the specific entity of agitation in patients with SAH and underscores its relevance in neurological patients.

Keywords Subarachnoid haemorrhage · Delirium · Microsurgical clipping · RASS · Neurocritical care · Hydrocephalus

Introduction

Aneurysmal subarachnoid haemorrhage (SAH) remains a life-threating disease with a mortality rate of up to 35% [30]. Rebleeding of the aneurysm, delayed cerebral ischaemia (DCI) and chronic hydrocephalus are well-studied complications resulting in increased mortality rates [14, 15, 30]. In addition, medical complications and systemic diseases affect the clinical course and outcome on the intensive care unit (ICU) [11]. A common problem of ICU patients is a hyperactive delirium (agitation) with an incidence of approximately 30% [1, 3, 23]. However, only limited data on this issue is published in SAH patients [6, 21, 22, 24]. The incidence of agitation in SAH patients ranges from 16.0 to 33.0% and was associated with intraventricular haemorrhage, hydrocephalus and a frontobasal haematoma [6, 21, 22]. Besides these SAH-related factors, psychiatric disorders and history of cocaine use are associated with agitation in SAH patients as well as endotracheal intubation, tissue damage, immobilization, noise and loss of day-night-rhythm in the overall group of ICU patients [20, 21].

Although delirium seems to be a common complication in SAH patients, screening for delirium in neurologically critically ill patients remains difficult since established screening tools are not validated sufficiently for neurocritical care patients so far [2, 9, 28]. The Richmond Agitation and Sedation Scale (RASS) [25] has been described once for a North-American SAH patient cohort with symptoms of agitation.

✉ Patrick Czorlich
p.czorlich@uke.de

[1] Department of Neurosurgery, University Medical Centre Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany

[2] Department of Intensive Care Medicine, University Medical Centre Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany

[21]. As the rate of agitation might vary between different populations and different treatment strategies in SAH patients, the aim of this study was to assess the rate of agitation and factors associated with the occurrence of an agitation in a European metropolitan vascular centre.

Methods

Patient selection and definition of hyperactive delirium

All patients admitted to our institution with proven SAH from 01/2012 to 01/2017 were eligible for this retrospective, anonymized study if a RASS value of 0 was documented at least once during the clinical course (Table 1).

Assessment and documentation of the RASS were performed at least every 8 h or in any change of the RASS by the nursing staff. The validity and reliability in evaluating the RASS by nursing staff were demonstrated already with the introduction of the RASS in 2002 [25].

Patients with at least one documentation of a RASS of ≥ 2 were counted to the hyperactive agitation group. If agitation occurred during and/or within 24 h after the analgo sedation was discontinued, it was counted as analgo sedation related. To assess if the occurrence of an agitation was related to a circadian dysrhythmia, times of agitation were dichotomized into daytime (8 a.m.–8 p.m.) and night-time (8 p.m.–8 a.m.).

Baseline characteristics

All clinical, medical historical and neuroradiological data were prospectively collected via clinical assessment and review of clinical documentation as described before [8]. Development of DCI was defined according to the definition of Vergouwen et al. [30]. The minimum and maximum plasma sodium levels were assessed at least three times/day. Mean plasma sodium values were calculated for each day (days 1–14) and used for further analysis.

Outcome was assessed at discharge, as well as on follow-up, and classified according to the Glasgow Outcome Scale (GOS) [16]. A GOS of 4 and 5 was defined as a favourable outcome. The study was reported to the local ethic committee of the state of Hamburg (WF-038/17) and formal consent was waived for this retrospective analysis which was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

Statistical analysis

Statistical analysis of the data was performed by a univariate analysis using two-sided Fisher's test, chi-squared test, Kruskal-Wallis test or ANOVA tests depending on the scale and distribution of the measurements to examine correlations between the parameters using IBM® SPSS® Statistics 22 (IBM Corporation, Armonk, NY, USA) and followed by a multivariate regression analysis. Outcome at discharge and follow-up was evaluated using Cox regression models. The level of statistical significance was set at $p < 0.05$.

Results

Baseline characteristics of the study population

Three hundred thirty-eight patients with aneurysmal SAH between 01/12 and 01/17 were screened for eligibility as described in the "Methods" section. Twenty-five patients were excluded for incomplete RASS values, while another 101 patients never reached an alert and calm status including 30 patients with best supportive care and an early case fatality within the first 7 days after admission leaving 212 patients showing at least one RASS of zero or higher during ICU stay (Fig. 1).

One hundred thirty-four (63.2%) patients were female. Mean age of this cohort was 54.9 ± 13.4 years. The average Hunt&Hess (H&H) grade was 2.5 (median of 2) and the mean Glasgow Coma Scale (GCS) was 12.5 (median of 15). Seventy-eight patients (36.8%) suffered from a hyperactive delirium out of the cohort that reached a RASS ≥ 0, while this rate dropped to 23.1% if all SAH patients in the given period would have been analysed. Detailed data of patients' clinical characteristics are provided in Table 2.

Occurrence of delirium

On average, the first signs of a hyperactive delirium occurred on day 10 and in 27 cases (34.6%) during weaning. Hyperactive delirium occurred on average after 2.8 ± 2.7 days and the duration of agitation ranged from 1 to 11 days. Univariate analysis revealed patients with a hyperactive delirium to have higher scores displaying disease severity (GCS, H&H, Fisher grade, Graeb score, SAPS II). Additionally, those patients had a higher frequency of initial hydrocephalus requiring ventriculostomy (Table 2).

The occurrence of the delirium did not correlate with day- or night-time but differed significantly between H&H grades with a higher incidence in more severe SAH ($p = 0.009$) (Fig. 2). Among multiple parameters, only patient's mean sodium levels turned out to be significantly different (univariate analysis) on 4 days with a higher level in patients with delirium ($p < 0.05$).

Treatment of the ruptured aneurysm and delirium

One hundred fifty-two patients (71.7%) of the study cohort underwent endovascular treatment of the ruptured aneurysm.

Table 1 Definition and distribution of the Richmond Agitation Sedation Scale [18]

Score	Term	Description
+ 4	Combative	Overtly combative or violent; immediate danger to staff
+ 3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behaviour towards staff
+ 2	Agitated	Frequent no purposeful movement or patient–ventilator desynchrony
+ 1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
− 1	Drowsy	Not fully alert, but has sustained (more than 10 s) awakening, with eye contact, to voice
− 2	Light sedation	Briefly (less than 10 s) awakens with eye contact to voice
− 3	Moderate sedation	Any movement (but no eye contact) to voice
− 4	Deep sedation	No response to voice, but any movement to physical stimulation
− 5	Unarousable	No response to voice or physical stimulation

Univariate analysis revealed that surgical treatment in patients with hyperactive delirium was more frequent compared to the group without hyperactive delirium (50.0 vs. 31.5%; $p = 0.011$) (Table 3).

According to local hospital protocols, hyperactive delirium was treated with haloperidol as antipsychotic drug, clonidine for vegetative symptoms and lorazepam for agitation with anxiety. For circadian resynchronization, melatonin was optionally given as an adjunctive medication. Second-line delirium therapy consisted of melperone, promethazine and olanzapine as antipsychotic drugs, and zopiclone, midazolam and diazepam as tranquillizing agents.

Multivariate regression towards occurrence of hyperactive delirium

All pre-existing conditions and treatment modalities which showed a p value below 0.1 in the univariate analysis were included in the regression model (Tables 2 and 3).

This analysis revealed the following four factors as independent risk factors for the development of a hyperactive delirium: initial hydrocephalus, microsurgical clipping, higher Graeb score and male gender (Table 4).

Functional outcome at discharge and follow-up

The overall hospital mortality rate was 4.2% ($n = 9/212$) in the analysed cohort with no significant difference between the subgroups ($p = 1.0$). Unfavourable outcome at discharge was determined in 81 patients (38.2%) of which 35 (43.2%) had a hyperactive delirium during ICU stay. A Cox regression analysis towards unfavourable outcome at discharge revealed no significant influence of hyperactive delirium ($p = 0.146$).

Neurological outcome data at follow-up was available for 158 of 212 patients (74.5%) after 165 ± 97 days (median 149 days). Unfavourable outcome occurred in 35 patients (22.2%). Thirteen (37.1%) of these patients suffered from a hyperactive delirium. Again, a Cox regression revealed no

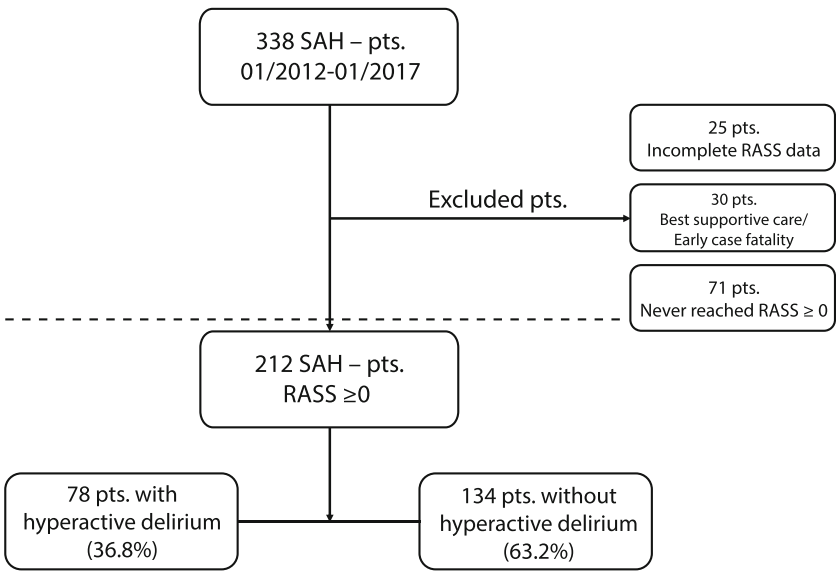

Fig. 1 Flow chart of patient exclusion and inclusion. pts patients, RASS Richmond Agitation and Sedation Scale, SAH subarachnoid haemorrhage

Table 2 Clinical and demographic characteristics

Characteristics	No delirium *n* = 134 (63.2%) Mean ± SD (range)	Hyperactive delirium *n* = 78 (36.8%) Mean ± SD (range)	*p* value
Age at SAH [years]	53.8 ± 13.4 (18–90)	56.6 ± 13.4 (29–83)	0.109
GCS	13.2 ± 3.5 (3–15) Median = 15	11.2 ± 4.6 (3–15) Median = 14	< 0.001
Hunt&Hess grade	2.3 ± 1.2 (1–5) Median = 2	2.9 ± 1.3 (1–5) Median = 3	0.001
Fisher grade	3.4 ± 0.9 (1–4) Median = 4	3.7 ± 0.7 (1–4) Median = 4	0.011
Aneurysm diameter [mm]	7.0 ± 4.6 (1.2–28.0)	6.2 ± 3.5 (2.0–22.7)	0.328
Number of aneurysms	1.3 ± 1.0 (0–6)	1.1 ± 0.4 (0–3)	0.182
Graeb score	2.8 ± 3.3 (0–14)	4.6 ± 3.7 (0–12)	0.001
Hijdra score	14.2 ± 8.4 (0–30)	15.4 ± 7.9 (0–30)	0.358
SAPS II	33.8 ± 11.6 (14–69)	39.2 ± 12.6 (17–71)	0.002
	Count (%)	Count (%)	
Sex			0.077
Female	91 (67.9)	43 (55.1)	
Male	43 (32.1)	35 (44.9)	
Aneurysm location			0.842
Anterior circulation	115 (85.8)	66 (84.6)	
Posterior circulation	19 (14.2)	12 (15.4)	
Initial hydrocephalus	74 (55.2)	64 (82.1)	< 0.001
Medical history			
Hypertension	53 (39.6)	36 (46.2)	0.388
Diabetes	4 (3.0)	2 (2.6)	1.0
Hyperlipidemia	10 (7.5)	7 (9.0)	0.794
Chronic headache	9 (6.7)	3 (3.8)	0.542
Cardiovascular disease	8 (6.0)	10 (12.8)	0.123
Pulmonic disease	13 (9.7)	12 (15.4)	0.270
Neurological disease	11 (8.2)	6 (7.7)	1.0
Nicotine abuse	26 (19.4)	18 (23.1)	0.599
Alcohol abuse	7 (5.2)	6 (7.7)	0.556
Hypothyroidism	9 (6.7)	6 (7.7)	0.787
Cancer	6 (4.5)	1 (1.3)	0.427
Psychiatric disorder	6 (4.5)	7 (9.0)	0.237
DCI	45 (33.8)	34 (43.6)	0.185

DCI delayed cerebral ischaemia, *GCS* Glasgow Coma Scale, *SAPS II* Simplified Acute Physiology Score

influence of hyperactive delirium towards unfavourable outcome ($p = 1.0$). Details are presented in Table 3.

Subgroup analysis of patient with microsurgical treatment

In a subgroup analysis, we investigated if surgery-related factors influenced the occurrence rate of a hyperactive delirium. In detail, we determined the duration of the procedure, use and dosage of barbiturate narcosis for neuroprotection, location of aneurysm, side of surgery and presence of ICH. Regression analysis identified no significant association of delirium with any of these factors. Only side of surgery showed a mild tendency to be associated with delirium since 61.5% of patients with a right side-located aneurysm developed a hyperactive delirium, compared to 38.5% of patients with a left side-located aneurysm ($p = 0.119$).

Discussion

Data about delirium in ICU patients with neurological diseases is scarce, as these patients are mostly excluded from general delirium studies performed at ICUs [2, 9, 29].

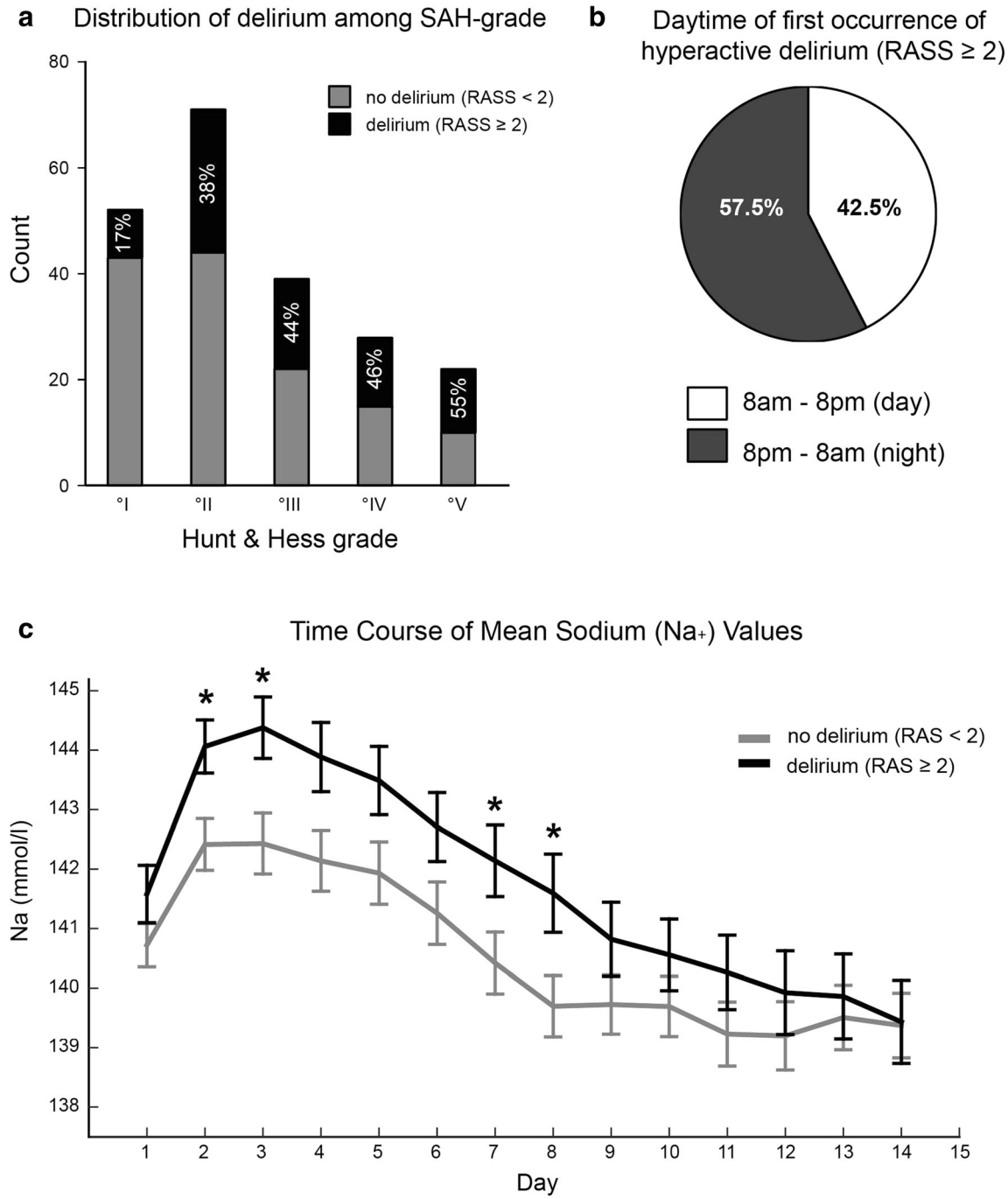

Fig. 2 **a** Distribution of hyperactive delirium among severity of the haemorrhage showing a higher occurrence of delirium in more severe SAH ($p = 0.009$). **b** Occurrence of delirium during day and night ($p = 0.242$). **c** Mean sodium values in both groups during the first 2 weeks on ICU (*$p < 0.05$)

Delirium in patients with SAH is a relevant complication during ICU treatment but relevant risk factors for the development of a hyperactive delirium and its functional consequences for neurological outcome are not well defined.

In this study, we found initial hydrocephalus, microsurgical clipping, a higher Graeb score and male gender to be independently associated with the development of agitation. Except for the gender, the identified risk factors might facilitate or result in agitation as the result of a more severe irritation of the brain parenchyma. However, in contrast to this hypothesis, our subgroup analysis revealed no causal link regarding surgery-related factors. Only right-sided surgery showed a tendency to an association without reaching statistical significance regarding the frequency of agitation. This is in line with previous clinical data and case reports showing that delirium is more common in right-sided brain damage [17, 18]. Data on delirium after neurosurgical procedures is rare, yet a significant frequency of delirium after craniotomy is reported [7, 12] and microsurgical

Table 3 Treatment and outcome

Characteristics	No delirium ($n = 134$) Mean ± SD (range)	Hyperactive delirium ($n = 78$) Mean ± SD (range)	p value
Duration of ventilation [h]	290.0 ± 301.0 (0–1039) $n = 78$	327.8 ± 304.8 (0–1196) $n = 52$	0.247
Days on ICU	18.2 ± 10.9 (1–54)	26.3 ± 13.2 (7–61)	< 0.001
Dexamethasone (mg)	58.7 ± 98.3 (0–496)	60.3 ± 93.4 (0–373)	0.235
	Count (%)	Count (%)	
Unfavourable outcome at discharge [GOS 1–3]	46 (34.3)	35 (44.9)	0.146
Unfavourable outcome at follow-up [GOS 1–3]	22 (22.2) $N = 99$	13 (22.0) $N = 59$	1.0
Treatment			0.011
Endovascular	104 (77.6)	48 (61.5)	
Microsurgical clipping	30 (22.4)	30 (38.5)	
Antipsychotic medication	30 (22.4)	70 (89.7)	< 0.001

GOS Glasgow Outcome Scale, *ICU* intensive care unit

clipping of the aneurysm turned out to be an independent risk factor for a hyperactive delirium in our SAH cohort as well.

In contrast to the previous studies on agitation in SAH, male patients in our cohort were at higher risk of developing agitation [6, 22]. Men were also more likely to experience postoperative delirium in other entities like hip fracture and vascular surgery [13, 19]. Surprisingly, age, pre-existing psychiatric diseases and nicotine or alcohol abuse were similar in both groups. This is in contrast to other studies, analysing postoperative delirium, in which age, alcohol and medical comorbidities are well-documented risk factors [22, 27]. These factors have been reported in a dissimilar patient cohort regarding socio-demographic factors (e.g., drug use, psychiatric disorders), which might explain the incongruent findings [22]. Hyperactive delirium was not an independent factor for unfavourable outcome neither at discharge nor follow-up in our study cohort. This can be interpreted in line with findings showing fluctuations of consciousness and duration of agitation having an inconclusive and inverse effect on outcome [21]. However, previous data of patients with traumatic brain injury or glioblastoma surgery suggested agitation as a predictor for poor neurological outcome after rehabilitation or decreased survival [4, 12, 26]. Nevertheless, these are distinct neurological disorders with completely different pathophysiology.

Table 4 Factors associated with hyperactive delirium (multivariate regression)

Characteristics	OR	CI	p value
Initial hydrocephalus	3.21	1.33–7.76	0.010
Microsurgical clipping	3.70	1.71–8.01	0.001
Graeb score	1.11	1.00–1.22	0.043
Male gender	1.97	1.09–3.85	0.047

CI confidence interval, *OR* odds ratio

Consistent with previous findings [6, 22], intraventricular haemorrhage was identified as a risk factor. In our study, we could demonstrate that not only the presence but also the amount of blood, using the Graeb score, correlated with the occurrence of delirium. This hypothesis was supported by our findings that delirium occurred more often in patients with a more severe SAH.

Plasma sodium levels were not independently associated with agitation and varied in a physiological range. Furthermore, the occurrence of agitation was independent of daytime in our study. Patients with a hyperactive delirium showed a significant longer stay on ICU and needed more antipsychotic medication. A recently published prospective randomized trial investigating the effect of prophylactic haloperidol in ICU patients failed to show a reduction in the occurrence of delirium in contrast to placebo, emphasizing the complex pathophysiology of delirium which presumably develops due to different pathophysiologic pathways and disturbed neurotransmitter levels [27, 29]. These inconclusive findings underline the need of further research investigating pathophysiological mechanisms and targets for treatment.

Methodological challenges and limitations

A major limitation of the presented study is its retrospective character, even though the RASS was obtained prospectively by trained nursing staff in a standardized way. To the best of our knowledge, no further delirium-screening tool is established and validated in patients with acute neurological disease [2, 10, 25]. Notably, the use of RASS as a screening tool for agitation in SAH patients is heterogenic as the definition of agitation was applied differently in a recent publication [21]. Reznik et al. defined agitation as a RASS ≥ 1 (restlessness) in contrast to our interpretation of the RASS with respect to the original definition as a score ≥

2. A recently reported screening tool in patients undergoing resection of a glioblastoma including factors like size of tumour or bihemispheric tumour involvement is obviously not applicable in SAH patients [12]. This demonstrates the necessity to evaluate and validate screening tools in patients with acute neurological disease. Furthermore, the exclusion of permanently unconscious patients in our study on the one hand might have biased the results. On the other hand, the inclusion of patients never reaching a calm and alert level might result in inverse findings. In this scenario, higher H&H grades might lower the risk of agitation, and therefore, the presence of agitation might be associated with a lower mortality risk. This problem points to another limitation: the evaluation and definition of a hypo dynamic delirium in patients with an acute neurological disease. It is a matter of opinion if the unconsciousness in acute neurologic patients is caused by the underlying brain damage, a multitude of medication effects and other factors or already fulfils the definition of a hypo dynamic delirium [21]. Although patients were treated according to hospital protocols, the use of benzodiazepines may be questionable as the guidelines available give contradictory recommendations in this regard [1, 5]. Nevertheless, it is unknown whether the recommendations concerning ICU-related delirium also apply to SAH-related delirium or whether the agitation has a different underlying pathophysiology and should be treated differently.

Conclusions

Our study provides four independent risk factors for the development of agitation in SAH patients. It emphasizes the specific entity of agitation in patients with primary brain injury. The pathophysiological mechanisms of hyperactive delirium and the effect on clinical outcome must be further evaluated. Since agitation in patients with brain injury may represent either a consequence of this injury or an independent type of delayed brain injury, the proper assessment and therapeutic consequences are largely unknown.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval The study was reported to the local ethic committee of the state of Hamburg (WF-038/17) and formal consent was waived for this retrospective analysis which was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

Informed consent Informed consent was waived by the local ethic committee as the present study was a retrospective analysis.

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