Summary

Introduction: Neurogenic pulmonary edema (NPE) is a clinical syndrome characterized by the acute onset of pulmonary edema after a significant central nervous system (CNS) insult. The most common neurological conditions associated with NPE are traumatic brain injury, subarachnoid hemorrhage (SAH), status epilepticus, meningitis or encephalitis, cerebrovascular insults. In patients with SAH, reports of NPE incidence range from 2% to 42.9%. NPE occurs as a consequence of releasing of catecholamines into the systemic circulation immediately after aneurysmal rupture. Clinically, the likelihood of developing NPE following SAH correlates with increasing age, delayed surgery, vertebral artery origin, and the severity of clinical and radiographic presentation (e.g. Hunt and Hess and Fisher grades).

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Key words: subarachnoid haemorrhage; neurogenic pulmonary edema; cardiac biomarkers; ECG changes

Introduction

Neurogenic pulmonary edema (NPE) is a clinical syndrome characterized by the acute onset of pulmonary edema after a significant central nervous system (CNS) insult. The most common neurological conditions associated with NPE are traumatic brain injury, subarachnoid hemorrhage (SAH), status epilepticus, meningitis or encephalitis, cerebrovascular insults. In patients with SAH, reports of NPE incidence range from 2% to 42.9%. NPE occurs as a consequence of releasing of catecholamines into the systemic circulation immediately after aneurysmal rupture. Clinically, the likelihood of developing NPE following SAH correlates with increasing age, delayed surgery, vertebral artery origin, and the severity of clinical and radiographic presentation (e.g. Hunt and Hess and Fisher grades).

Since the catecholamines have direct effect on the myocardium, the aim of this study is to investigate a possible correlation between the value of cardiac biomarkers on admission and incidence of NPE in patients with aneurysmal SAH.
Material and Methods

From August 2009 to January 2014, the study enrolled 262 consecutive patients admitted to the Neurosurgery Clinic. Inclusion criteria for the study were patients ≥ 18 years of age and the diagnosis of aneurysmal SAH confirmed by cerebral computed tomography (CT) scanning and CT angiography. If the CT angiogram was negative and the suspicion of aneurysm existence was high, the CT angiography was repeated two days later. The inclusion criterion was also the time interval between SAH onset and hospital admission below 96 hours. Chest X-rays were obtained immediately for those suspected of having SAH. Patients with a history of myocardial infarction, cardiomyopathy, or congestive heart failure were excluded from the study.

The study protocol was approved by the Ethics Committee of the School of Medicine, University of Belgrade (No 440/VI-11), and informed consent was obtained from each patient or an appropriate designee. The identity of the enrolled patients was protected. Any clinical procedure was performed in accordance with institutional guidelines. Demographic and clinical data were collected from patient and family interviews and by the review of medical records after enrolment. These data included age, sex, and risk factors for coronary artery disease (CAD). Heart rate (HR) and systolic blood pressure (SBP) on admission were recorded.

The severity of neurological injury was graded using each subject’s admission Hunt and Hess and Fisher grade. Patients with Hunt and Hess grades I and II were admitted to the neurosurgery ward while those with Hunt and Hess grades III-V to the neurosurgical intensive care unit (NICU).

Clinical management

Every patient was examined daily for the occurrence of NPE. Clinical criteria for NPE included the presence of crackles that suggested fluid in the lungs and presence of frothy pink tracheal fluid. Radiographic criteria for NPE included sharply defined pulmonary markings accompanied by blurring or haziness of the perivascular outlines and loss of demarcation of hilar shadows. All chest X-rays were interpreted by board-certified radiologists blinded to the clinical symptoms of the patient. Patients who fulfilled both clinical and radiographic criteria were diagnosed with NPE. Among the 262 SAH patients, 19 (7.25%) developed NPE. In patients with NPE, arterial blood gas analysis was performed and the type of respiratory support was determined. The time of occurrence of NPE from SAH attack was noted.

The need for inotropic or vasopressor support and time of initiation were documented.

All NICU patients had continuous electrocardiographic (ECG) monitoring and noninvasive blood pressure monitoring (NIBP), as a part of the standard clinical practice. Although central venous catheters were placed routinely, pulmonary artery catheters were not placed. Modified triple-H therapy was initiated in patients with symptomatic vasospasm. The patients were kept normovolemic. In case a patient needed continuous sedation in NICU, Midazolam (0.1–0.2 mg/kg/h) in combination with Remifentanil (0.05–0.2 μg/kg/min) was used. Endotracheal intubation and mechanical ventilation were performed when clinically indicated.

Serum cardiac and inflammatory biomarkers

Each subject was assessed on the day of enrollment. The subjects with NPE were assessed also on the day when NPE was clinically and instrumentally diagnosed.

On each study day, the following biomarkers of cardiac injury and inflammatory biomarkers were measured: creatine phosphokinase (CPK), creatine phosphokinase MB isoenzyme (CPK-MB), creatine phosphokinase MB mass concentration (CPK-MB mass), myoglobin, and cardiac troponin I (TnI), C-reactive protein (CRP), white blood cells (WBC) count, and blood glucose level.

The levels of biomarkers were then dichotomized as elevated for levels exceeding the following values: CPK > 150 IU/L in women and 200 IU/L in men, CPK-MB > 24 IU/L, CPK-MB mass > 5 ng/mL, TnI > 0.04 ng/mL, myoglobin > 110 ng/mL, CRP > 5 mg/L and WBC count > 9.7 x 10^9/L, as well as blood glucose level > 6.1 mmol/L. These cut-offs are adopted according to referent values from our biochemical laboratory.

The time from SAH symptoms onset to measurement of biomarkers was recorded for every patient and it was less than 96 hours.

Neurological assessment

Every patient was neurologically examined in search for signs of hydrocephalus, delayed cerebral ischemia (DCI) or re-rupture. In case of neurological deterioration, a CT scan was performed.
Statistical analysis

262 patients were dichotomized based on the development of NPE. Data were described by frequency and percentage in case of categorical variables, while mean and standard deviation (SD) were run for continuous variables. Data with normal distribution were assessed by Kolmogorov-Smirnov test. For the comparison between NPE+ and NPE− groups, chi-square or Fisher’s exact test were used for categorical variables, while the unpaired t-test or Mann-Whitney U test were used for continuous variables where appropriate. Univariate and multivariate logistic regression analysis were used to identify variables predictive of NPE+ outcome. Pearson’s correlation between all potential predictors was examined. SPSS 22 (IBM, Chicago, Illinois) was used for statistical analysis and p < 0.05 was considered statistically significant.

Results

The study included 262 subjects, of which 7.25% (19 subjects) developed NPE. The total number of examined SAH patients was 368. The number of excluded patients was 106 (28.8%) and the reasons of exclusion are shown on picture 1.

As shown in table 1, the mean age of the 19 study subjects who developed NPE was 52.4 ± 9.5 years. The mean age of 243 subjects who didn’t develop NPE was 52.2 ± 11.1 years. There were 84.2% of patients with NPE were women and 60.1% of patients without NPE were women (P = 0.037). The patients who developed NPE had more severe SAH (Hunt and Hess grade > 2), 94.7 vs. 63.0. The mean peak SBP on admission and the heart rate were similar in patients with and without NPE, but history of hypertension (HTA) was more common in patients with NPE (63.2 vs. 36.2, P = 0.02).

Comparison of radiological characteristics (Table 2) revealed similar occurrence of NPE in patients with Fisher grade ≤ 2 and > 2 (63.4 vs. 84.2) (deleted: P = 0.067). However, patients with NPE had higher mean Fisher grade that the group without NPE (3.36 ± 0.76 vs. 2.86 ± 0.84, P = 0.11).

The occurrence of NPE was higher in patients with elevated values of all cardiac biomarkers (Table 3). Elevated WBC count were common in patients who developed NPE (P < 0.001). Among neurological characteristics, none of them were statistically significant in patients with NPE comparing to patients without NPE.

The univariate relationships between the predictor variables and NPE, as determined by logistic regression are shown in Table 3. A Hunt-Hess grade of ≥ 3, female, history of HTA, hydroceph-
Table 1: Comparison of demographic and clinical variables and risk factors for CAD between SAH patients with and without NPE on admission

|                     | Pts with NPE (N = 19) | Pts without NPE (N = 243) | p^b |
|---------------------|-----------------------|---------------------------|-----|
| **Age (mean ± SD), y** | 52.4 ± 9.5            | 52.2 ± 11.1               | 0.943 |
| **Female sex, n (%)**       | 16 (84.2)             | 146 (60.1)                | 0.037^a |
| **Clinical characteristics** |                      |                           |     |
| Hunt and Hess ≥ 3, n (%)   | 18 (94.7)             | 153 (63.0)                | 0.005^a |
| SBP (mean ± SD), mmHg      | 155 ± 19.4            | 148 ± 24.7                | 0.251 |
| HR (mean ± SD), min^-1     | 79.7 ± 18.5           | 82.3 ± 15.8               | 0.512 |
| Admission on day of SAH attack, n (%) | 13 (68.4) | 116 (47.7)                | 0.082 |
| **Risk factors for CAD, n (%)** |                     |                           |     |
| History of hypertension  | 12 (63.2)             | 88 (36.2)                 | 0.020^a |
| History of diabetes      | 2 (10.5)              | 44 (18.1)                 | 0.403 |
| History of hyperlipidemia| 6 (31.6)              | 71 (29.2)                 | 0.828 |
| History of smoking       | 2 (10.5)              | 60 (24.7)                 | 0.505 |
| Family history of CAD    | 6 (31.6)              | 62 (25.5)                 | 0.561 |

SAH – subarachoid haemorrhage; NPE – neurogenic pulmonary edema; SBP – systolic blood pressure; HR – heart rate; CAD – coronary artery disease; SD – standard deviation

^aStatistically significant
^bAccording to chi-square, Student’s t-test or Mann-Whitney U test where appropriate

Table 2: Comparison of radiological and neurosurgical variables between SAH patients with and without NPE on admission

|                     | Pts with NPE (N = 19) | Pts without NPE (N = 243) | p^b |
|---------------------|-----------------------|---------------------------|-----|
| **Radiological characteristics** |                      |                           |     |
| Fisher > 2, n (%)    | 16 (84.2)             | 154 (63.4)                | 0.067 |
| Anterior circulation aneurysm location, n (%) | 17 (89.5) | 216 (88.9)                | 0.938 |
| Multiple aneurysms, n (%) | 2 (10.5)              | 26 (10.7)                 | 0.981 |
| **Neurosurgical characteristics** |                     |                           |     |
| Secured aneurysm, n (%) | 13 (68.4)             | 201 (82.7)                | 0.121 |
| Hydrocephalus, n (%) | 9 (47.4)              | 66 (27.2)                 | 0.061 |
| Rerupture, n (%)     | 5 (26.3)              | 43 (17.7)                 | 0.350 |
| Seizures, n (%)      | 5 (26.3)              | 48 (19.8)                 | 0.493 |
| Secured aneurysm, n (%) | 13 (68.4)             | 201 (82.7)                | 0.121 |

SAH – subarachoid haemorrhage; NPE – neurogenic pulmonary edema

^aStatistically significant
^bAccording to chi-square, Student’s t-test or Mann-Whitney U test where appropriate (deleted)
alus, ST-T changes, prolonged QTc interval were all significant predictors of NPE. Elevated values of cardiac biomarkers were significantly more frequent in patients with NPE (P ranged from < 0.001 to 0.017).

Between all the potential predictors examined in univariate logistic regression analysis, we explored Pearson's correlation and found that there is statistically significant correlation between categorical equivalents of cardiac biomarkers (troponin I, myoglobin, CPK, CPK-MB and CPK-MB mass) (r ranged from 0.158 to 0.836, P from < 0.001 to 0.010). Also, we found statistically significant correlation between WBC count, elevated WBC count and CRP (r ranged from 0.316 to 0.816, P < 0.001) and statistically significant correlation between ST-T changes and prolonged QTc (r = 0.611, P < 0.001).

Some of the variables we used are highly correlated, so we didn't include all of them in the multiple regression analysis with intention to avoid a phenomenon of multicollinearity. The consequence of multicollinearity is that coefficient estimates are unstable and difficult to interpret. So

### Table 3: Comparison of biohumoral variables between SAH patients with and without NPE on admission

| Biohumoral characteristics | Pts with NPE N = 19 | Pts without NPE N = 243 | p<sup>b</sup> |
|-----------------------------|---------------------|-------------------------|---------------|
| Troponin I, (mean ± SD), ng/mL, median (IQR) | 0.123 ± 0.187 0.064 (0.03–0.12) | 0.244 ± 0.88 0.02 (0.01–0.05) | < 0.001<sup>a</sup> |
| Elevated troponin I, n (%) | 14 (73.7) | 68 (28.0) | < 0.001<sup>a</sup> |
| Myoglobin (mean ± SD), ng/mL median (IQR) | 220.4 ± 96.4 213 (146–268) | 153.6 ± 114.6 124.5 (86–179) | < 0.001<sup>a</sup> |
| Elevated myoglobin, n (%) | 18 (94.7) | 151 (63.2) | 0.004<sup>a</sup> |
| CPK (mean ± SD), IU/L, median (IQR) | 262.7 ± 115 236 (194–310) | 129.5 ± 91.3 98 (69–164) | < 0.001<sup>a</sup> |
| Elevated CPK, n (%) | 17 (89.5) | 57 (23.5) | < 0.001<sup>a</sup> |
| CPK-MB (mean ± SD), IU/L, median (IQR) | 22.8 ± 7.8 22 (17–27) | 13.9 ± 6.6 12 (9–18) | < 0.001<sup>a</sup> |
| Elevated CPK-MB, n (%) | 7 (36.8) | 20 (8.2) | < 0.001<sup>a</sup> |
| CPK-MB mass (mean ± SD), ng/mL median (IQR) | 4.3 ± 1.5 4 (3–5) | 2.8 ± 1.4 3 (2–4) | < 0.001<sup>a</sup> |
| Elevated CPK-MB mass, n (%) | 3 (15.8) | 9 (3.7) | < 0.001<sup>a</sup> |
| White blood cells count (mean ± SD), 10<sup>9</sup>/L median (IQR) | 13.4 ± 2.7 12.7 (11.9–14.8) | 9.5 ± 4.3 8.4 (6.4–12.3) | < 0.001<sup>a</sup> |
| Elevated white blood cells count, n (%) | 17 (89.5) | 91 (37.4) | < 0.001<sup>a</sup> |
| Blood glucose(mean ± SD), mmol/L, median (IQR) | 8.3 ± 1.9 8.3 (6.9–9.6) | 8.4 ± 2.8 7.8 (6.3–9.8) | 0.740 |
| Elevated blood glucose, n (%) | 17 (89.5) | 193 (79.4) | 0.290 |
| C-reactive protein (mean ± SD), mg/L median (IQR) | 10.3 ± 12.4 7.1 (3.6 – 9.6) | 5.8 ± 4.7 4.7 (10.3–21.6) | 0.094 |
| Elevated C-reactive protein, n (%) | 11 (57.9) | 110 (45.3) | 0.288 |

SAH – subarachoid haemorrhage; NPE – neurogenic pulmonary edema; SD – standard deviation; IQR – interquartile range; CPK – creatine phosphokinase; CPK-MB – creatine phosphokinase MB isoenzyme; CPK-MB mass – mass creatine phosphokinase MB mass concentration

<sup>a</sup>Statistically significant

<sup>b</sup>According to chi-square, Student's t-test or Mann-Whitney U test where appropriate
we took one of the variables from each group (elevated troponin I, elevated WBC count and ST-T changes) and put them into the multivariate model together with age, female sex and variables which in univariate model had $P < 0.100$ (Hunt and Hess grade $\geq 3$, history of HTA and hydrocephalus).

**Table 4:** Univariate logistic regression analysis to identify variables predictive of NPE associated with SAH

| Predictors                      | OR   | 95% CI      | P     |
|---------------------------------|------|-------------|-------|
| Age, years                      | 1.002| 0.96–1.04   | 0.943 |
| Female sex                      | 3.540| 1.01–12.48  | 0.049a|
| Hunt and Hess grade $\geq 3$    | 10.992| 1.43–84.10 | 0.021a|
| Anterior circulation aneurysms  | 0.835| 0.18–3.85   | 0.817 |
| History of HTA                  | 2.785| 1.05–7.39   | 0.040a|
| Hydrocephalus                   | 2.378| 0.92–6.17   | 0.075 |
| Troponin I (elevated)           | 7.300| 2.50–21.24  | 0.000a|
| Myoglobin (elevated)            | 11.959| 1.57–91.13 | 0.017a|
| CPK (elevated)                  | 24.672| 5.47–111.17| 0.000a|
| CPK-MB (elevated)               | 6.476| 2.24–18.68  | 0.001a|
| CPK-MB mass (elevated)          | 4.815| 1.14–20.19  | 0.032a|
| White blood cells count (elevated) | 15.282| 3.42–68.22 | 0.000a|
| Blood glucose level (elevated)  | 2.508| 0.55–11.31  | 0.232 |
| C-reactive protein (elevated)   | 1.645| 0.63–4.26   | 0.306 |

CI – confidence interval; OR – odds ratio; NPE – neurogenic pulmonary edema; SAH – subarachnoid haemorrhage; HTA – hypertension; CPK – creatine phosphokinase; CPK-MB – creatine phosphokinase MB isoenzyme; CPK-MB – mass creatine phosphokinase MB mass concentration

*aStatistically significant

**Table 5:** Multivariate logistic regression analysis to identify variables predictive of NPE associated with SAH

| Predictors                      | OR   | 95% CI      | P     |
|---------------------------------|------|-------------|-------|
| Age, years                      | 0.997| 0.94–1.06   | 0.933 |
| Female sex                      | 5.253| 1.14–24.16  | 0.033a|
| Hunt and Hess grade $\geq 3$    | 12.593| 1.27–124.79| 0.030a|
| History of HTA                  | 3.922| 1.07–14.39  | 0.039a|
| Hydrocephalus                   | 2.028| 0.61–6.67   | 0.244 |
| Troponin I (elevated)           | 4.862| 1.26–18.74  | 0.022a|
| White blood cells count (elevated) | 21.867| 4.02–118.75| <0.001a|

CI – confidence interval; OR – odds ratio; NPE – neurogenic pulmonary edema; SAH – subarachnoid haemorrhage; HTA – hypertension

*aStatistically significant
After statistical adjustment by multivariate logistic regression (Table 5), elevated TnI (odds ratio (OR) 4.862 per quintile; 95% confidence interval (CI) 1.26–18.74, P = 0.022), elevated WBC count (OR 21.867; 95% CI 4.02–118.75, P < 0.001), being female (OR 5.253; 95% CI 1.14–24.16, P = 0.033), Hunt and Hess of ≥ 3 (OR 12.593; 95% CI 1.27–124.79, P = 0.030), and presence of HTA (OR 3.922; 95% CI 1.07–14.39, P = 0.039), independent risk factors of NPE were established.

Discussion

The incidence of NPE after SAH in our cohort of 262 patients is 7.25%, which is comparable with that reported in the literature (2–42.9%)1–10. ECG abnormalities and myocardial enzyme release after SAH are well-known and described15–17, but the relative contribution of cardiac dysfunction in the pathogenesis of NPE has been unclear. The pathophysiology of NPE is multifactorial. There is evidence that in a subset of patients, neurologic insult leads to direct myocardial injury and the development of NPE. Although the cardiac injury after SAH is more severe in patients who developed NPE, measurement of serum cardiac biomarkers with intention to explore risk factors for occurrence of NPE has rarely been conducted8,18,19.

In our study, none of the patients on admission had NPE. In study of Inamasu et. al.18, 11% of the patients were diagnosed with NPE on admission. The lower incidence of NPA in our study could be due to early initiated diuretic therapy (50.8% of all patients) and above all because of early enrollment.

According to the results of demographic comparison (Table 1), NPE was a more common finding in the subgroup of patients with clinically severe hemorrhage (Hunt and Hess grade III–V)6,8,16. All patients with NPE presented with radiologically severe bleeding (Fisher grade III, IV), as expected8. Although previous studies showed that ruptured posterior circulation was a risk factor for NPE6,8, the location of aneurysm was not associated with NPE in our study. The lack of statistical difference in our study may also be attributable to the pre-hospital death of those patients.

Higher number of patients with SAH which complicated with NPE had elevated values of cardiac biomarkers levels on admission, and the result is in concordance with the cardiac key role in pathogenesis of NPE6,10,18,19. Since cardiac biomarkers were positively correlated, most patients complicated by NPE exhibited a concomitant increase in all of these cardiac biomarkers levels.

Univariate logistic regression analysis revealed that elevated levels of cardiac biomarkers on admission are risk factors for NPE. The elevated values of TnI were significantly more common in patients who would develop NPE which is confirmed by previous studies8,10,16,18. The important fact in our study is that none of our patients on admission had NPE. Our clinic is tertiary health center, so very often the SAH therapy has initiated before patient’s admission and that can be the cause of our results.

The possibility of prediction of NPE by the elevated WBC is proved in studies where NPE is prevented by attenuating inflammation20–22. Finally, multivariate logistic regression analysis verified that elevated TnI and WBC count are risk factors for NPE.

There are several limitations in our study. First, we had no possibility to use transthoracic echocardiography (TTE) examination of the heart structure and function. This could enable to assess role of the heart dysfunction in pathophysiology of NPE23. Zaroff et al.10 found that the great majority of patients with NPE were complicated by concomitant wall motion abnormality. In another study, Inamasu et al.6 also found that 88% of the patients with NPE had also Takotsubo cardiomyopathy. Tung et al. revealed that 23% of patients with regional wall motion abnormalities had pulmonary edema24. Secondly, a different time from SAH onset to admission at the hospital could also have influenced the results. Third, we had only one measurement for the examined variables which are measured within 96 hours of SAH onset. The results of this study although interesting should be viewed cautiously because of the low number of patients identified with NPE.

Despite these limitations, this study is unique because cardiac biomarkers on admission in prediction of SAH-induced NPE were evaluated for the first time, and we believe that it might provide a new insight into the pathogenesis, however further evaluation is needed.

Conclusions

The elevated values of cardiac biomarkers on admission appear to play an active role as risk factors for NPE. Although we didn’t use TTE examination in our study, we recommend it to confirm or exclude global or regional left ventricular systolic dysfunction and to ensure that therapeutic decisions are based on the cardiac status of each patient.
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