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Cardiac dysfunction evoked by ECG and echocardiography changes and release of cardiac biomarkers in patients with aneurysmal subarachnoid haemorrhage. Case presentation and literature review

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ABSTRACT

The invisible brain-heart link has been observed and described for centuries now, although a greater interest in the matter has been manifested over the past several decades, especially in patients with aneurysmal subarachnoid haemorrhage (aSAH). We present the case of a patient with aSAH and signs of cardiac injury evoked by ECG changes and elevated cardiac enzymes. Furthermore, we reviewed current medical literature by searching the international database PubMed for recent articles on the subject of cardiac biomarkers, ECG and echocardiography changes in the setting of SAH. Our analysis of the selected articles, published between 2012 and 2018, revealed that 22 are patient population studies, 16 are case studies and 6 are reviews of the literature. The most common ECG changes were prolonged QTc andnonspecific ST/T-wave changes. Echocardiography changes included regional wall-motion abnormalities, typically involving the base of the heart (neurogenic stunned myocardium), yet there was also the scenario of Takotsubo cardiomyopathy (stress cardiomyopathy), which affects the apex of the heart. There is a significant statistical association of elevated levels of troponin and NT-proBNP with a bad outcome after SAH, and we should always keep in mind the dramatic scenario of misdiagnosing the cerebral haemorrhage and treating for a coronary syndrome instead. Therefore, the management of aSAH requires a close cooperation between neurosurgeons, intensivists, cardiologists and radiologists in high volume centres.

INTRODUCTION

Cardiac dysfunction in patients with an intracranial pathology represents a well-known complication and a pressing problem for both neurosurgeons and intensivists treating such a patient. The matter is

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probably best described for cases of subarachnoid hemorrhage (SAH), which account for approximately 10% of all strokes. Most SAHs are caused by ruptured saccular (berry) aneurysms.

This is a devastating clinical event, with a high mortality rate - average case fatality of 51%, as well as substantial neurologic morbidity in survivors (1-7).

The complex interactions between the affected brain and the heart are responsible for unique cardiovascular morbidity and mortality - up to 23% of deaths caused by cardiovascular and pulmonary complications (1)(8)(9). A number of cardiac changes occur in the acute phase of SAH, including ECG changes, structural changes on echocardiography, and acute troponin and NT-proBNP elevations (3)(10-16).

Case presentation

A 47-year-old man, with a medical history of hypertension, was brought to the emergency department in Pitesti for repetitive generalized seizures. Upon presentation, he had a Glasgow Coma Scale of 5 (E1, V1, M3), therefore he was sedated and intubated. His wife told the doctors that a few hours earlier he had complained of a severe headache, followed by a reduction in visual acuity for the left eye. Moreover, 2 weeks back, he had presented another severe headache and vomiting. The head CT revealed an interhemispheric hemorrhage and a right-sided fronto-temporo-parietal subdural hematoma. The patient was then transferred to the University Emergency Hospital in Bucharest. Upon admission, he was sedated, with a GCS of 3, anisocoria (mydriasis of the right eye) and left hemiplegia; he was intubated and mechanically ventilated and cardiovascularly stable, with a normal ECG (Fig. 1). An emergency angiography revealed a ruptured aneurysm on the anterior communicating artery, which was embolized. The subdural hematoma was also evacuated.

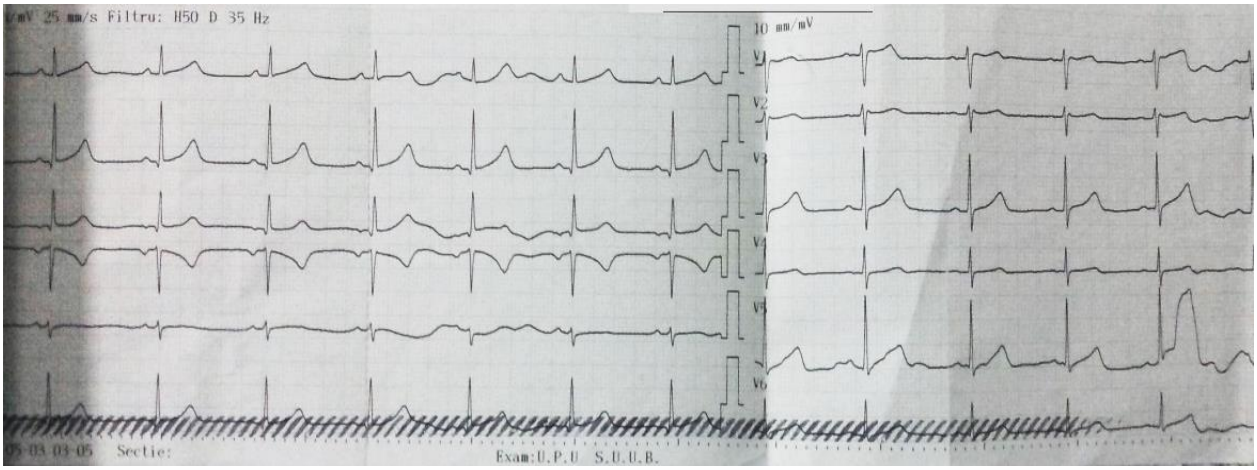

Figure 1. Normal ECG upon admission

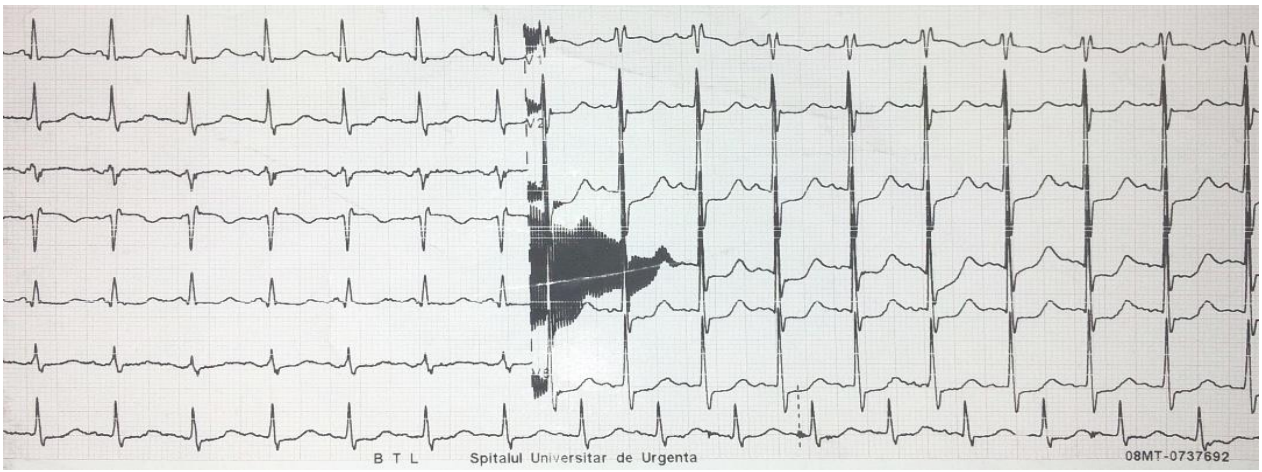

Figure 2. ST segment depression in the anterolateral territory (V2-V6)

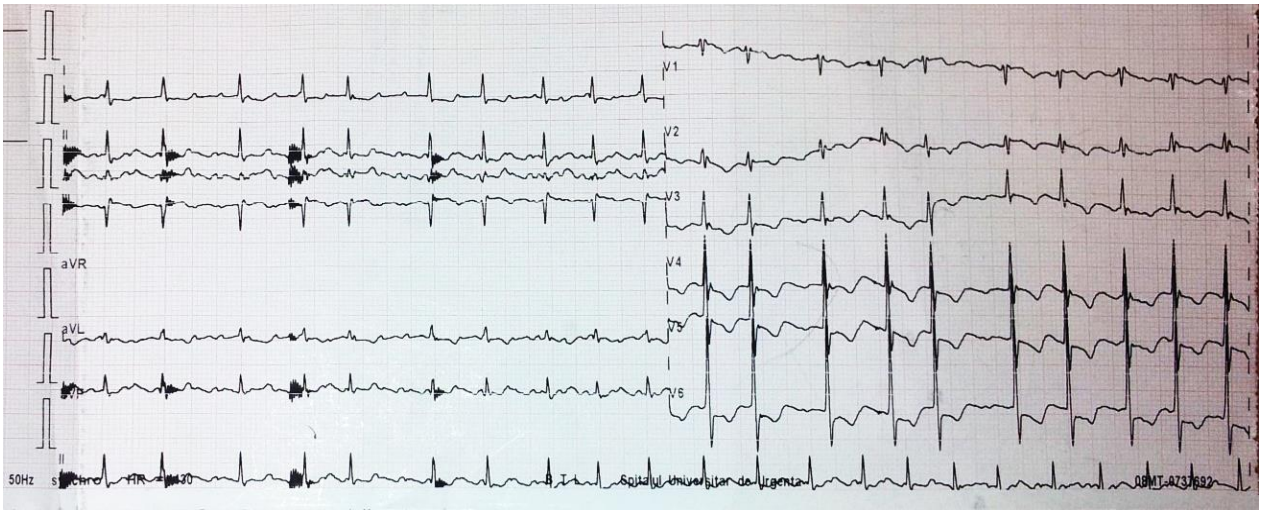

FIGURE 3. Atrial flutter, with variable atrio-ventricular block, and antero-lateral ST depression

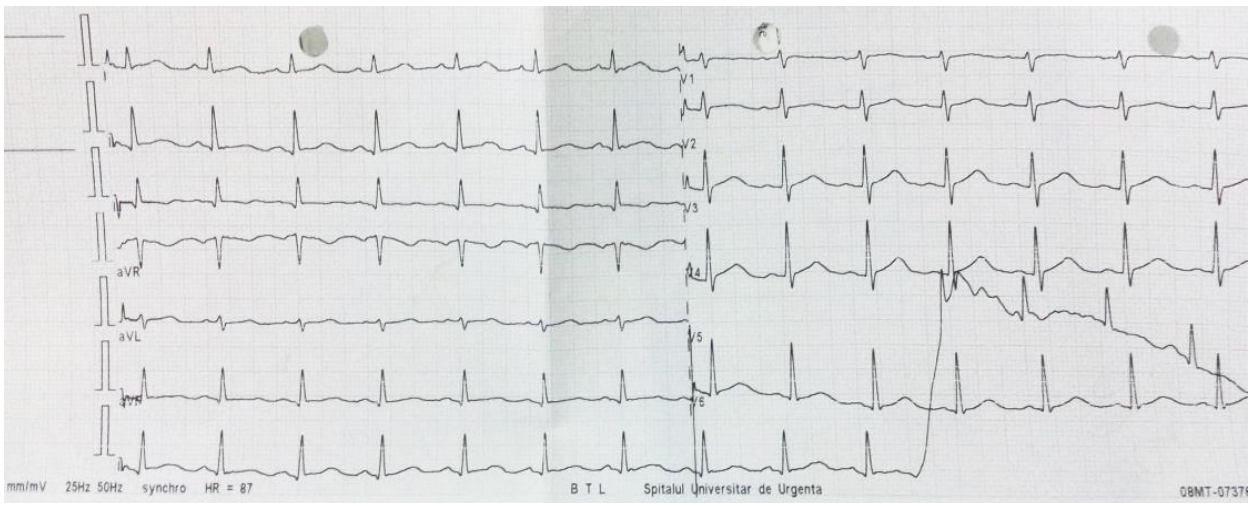

FIGURE 4. T wave flattening in DII, DIII, aVF, V1-V2 and V6

On the third day, the patient was neurologically better – a CGS of 8 (E2, V1, M5), maintaining left hemiplegia, yet still intubated and mechanically ventilated, with an arterial pressure of 105/65 mmHg, tachycardic 108 bpm. His ECG started changing, at first with ST segment depression in V2-V6 (antero-lateral territory), followed by atrial flutter, with variable atrioventricular block, and anterolateral ST depression (Fig. 2,3). Cardiac enzymes were also high – CK 807 U/L, CKMB 105 U/L, troponin I 1,5 ng/ml and NT-proBNP 173 pg/ml, with normal creatinine clearance and electrolytes. On echocardiography, there was a normal left ventricular ejection fraction and no wall-motion anomaly, thus the scenario was interpreted by the cardiologist as neurologically mediated. CK (1262 U/L) and CKMB (203 U/L) reached their peak value 8 hours later, while troponin had a maximum value of 8,26 ng/ml approximately 20 hours later.

A repeated head CT on day 5 revealed a frontal intraparenchymal hemorrhage of 55/14 mm in axial plane and 27 mm cranio-caudal and a bilateral frontal cortico-subcortical ischemic area in the vascularisation territory of the anterior cerebral artery. The vasospasm was confirmed by 2 subsequent angiographies performed on day 5 and 7, when Nimotop (nimodipine) was also locally injected.

CK and CKMB normalized on day 5, while troponin I normalized on day 7. On day 36, the patient was conscious, with a CGS of 13-14 (E 4 V 3-4, M 6) and a residual left hemiparesis, spontaneously

breathing, cardiovascularly stable and a relatively normal ECG (T wave flattening in DII, DIII, aVF, V1-V2 and V6) (Fig. 4).

Material ad method for the literature review

We queried the international database PubMed for recent articles using the syntax: subarachnoid [title/abstract], hemorrhage [title/abstract], cardiac [title/abstract], restricted with filters: publication date from 2012/01/01 to 2018/04/01; humans. Afterwards we selected 44 articles tackling the aspects of raised levels of troponin and NT-proBNP and ECG and echocardiography changes in patients with SAH.

Results

Our analysis of the selected articles revealed that 22 are patient population studies, 16 are case series and 6 are reviews of the medical literature.

ECG abnormalities

Jeong et al., in a study of 122 patients with SAH and no previous heart disease (62% women) [17] aimed to determine the frequency, influencing factors and impact on outcome of cardiac arrhythmias after aSAH. 50% of their population had a clinically significant ECG change, the most common type being nonspecific ST-T changes. A multivariate analysis showed no significant association of various factors (age, sex, Hunt-Hess grade, Fisher grade, hypertension, symptomatic vasospasm and ICU length of stay) with clinically significant arrhythmia. Yet, the presence of ECG changes wasindependently predictive of death and poor outcome. On the other hand, July et al. (18) managed to demonstrate that ECG abnormalities were significantly associated with total cortisol an day 4 and free cortisol on day 2, while Amin et al. (19) observed a statistically significant association between SAH and QTc prolongation.

Prolonged QT was the most prevalent ECG change in 413 patients from CONSCIOUS-1, a prospective randomized trial of clazosentran for the prevention of angiographic vasospasm (10). In this group of patients, the authors tried to identify ECG changes associated with angiographic vasospasm following SAH and concluded that, on multivariate analysis, QT prolongation and tachycardia are both associated with this complication. Moreover, tachycardia and ST changes were associated with worse clinical outcome.

In another large prospective study - 447 SAH patients, Schmidt et al. (20) confirmed that uncontrolled prolonged heart rate elevation (PEHR) is associated with an increased risk of major cardiopulmonary events: hypertension and hypotension requiring vasoactive therapy, pulmonary edema, myocardial injury evidenced by troponin I elevation and poor outcome. 39% of their patients developed PEHR (heart rate of at least 95 beats/minute, for more than 12 hours), with 68% of them having late-onset PEHR (more than 72 hours after SAH onset), which was correlated with an increased risk of delayed cerebral ischemia from cerebral vasospasm. Multifactorial logistic regression revealed the factors associated with PEHR: nonwhite race, Hunt-Hess score of at least 4 at admission, high admission APACHE-2 score and modified Fisher score. In this study, pre-hospital beta-blocker use was protective against PEHR.

By contrast, in a retrospective review of 254 patients with SAH, Crago et al. found (21) no relationship between the pre-hospital use of ACE inhibitors and/or beta-blockers and the development of pulmonary congestion, elevation in troponin or CKMB, heart rate, ECG changes or echocardiography findings. Moreover, a relationship was described between the use of these drugs and arrhythmias (ventricular or supraventricular) recorded by Holter monitoring, with patients taking beta-blockers.

A study from Japan (22) draws attention on the clinical scenario of comatose patients resuscitated from SAH-associated out-of-hospital cardiac arrest (OHCA) (SAH-OHCA) who often have clinical signs that mimic acute coronary syndrome-associated OHCA (ACS-OHCA) patients. As the management of SAH is totally different from that for ACS, doctors should be able to differentiate between the two as quickly as possible. Yamashina et al.analysed the retrospective data of 1259 consecutive OHCA and included in their study 23 resuscitated comatose ACS-OHCA patients and 20 resuscitated comatose SAH-OHCA patients. ST-T abnormalities on the ECG suggesting myocardial damage were noted in most patients in both groups (95% in the ACS-OHCA and 85% in SAH-OHCA), yet reciprocal ST depression was significantly more often absent in the SAH-OHCA group. Moreover, pulseless electrical activity (PEA) or asystole as the initial cardiac rhythm, female gender, and preserved left ventricular ejection fraction were

significantly more common in the SAH-OHCA group. In their group, initial PEA/asystole and presence of 1 other factor was sufficient to differentiate between SAH and ACS-OHCA patients (100% sensitivity, 91% specificity, 95% accuracy).

Almost all the 16 case reports also point to the possibility of SAH masquerading as an ACS (23-36). One of them presents the scenario of SAH with the pattern of sinus node dysfunction on the ECG (37), while Elsharkawy et al., on a cohort of 20 SAH patients observed that patients with fluctuating ECG changes had a poor outcome compared with patients with fixed abnormalities (38).

Troponin and NT-proBNP elevation

In a retrospective review of 617 patients with aSAH conducted by Ahmadian et al. (13), 14.1% (87 patients) required a cardiac evaluation: 63% had arrhythmia, 47% suffered a myocardial infarction and 31% developed heart failure. The majority of cases with a myocardial infarction (90.2%) were non-ST elevation MI, while atrial fibrillation was the most common form of tachyarrhythmia described. Among the patients who had a cardiac event at the time of a SAH, those with myocardial infarction, and in particular those with a troponin level greater than 1 mcg/L had a 10 times higher risk of death.

Oras et al. (11), in a single-centre prospective observational study including 126 SAH patients, managed to conclude that both peak levels of troponin (hsTnT in their study) and NT-proBNP are independently associated with cerebral infarction due to delayed cerebral ischemia. hsTnT had its peak level at admission followed by a daily decline; by contrast, NT-proBNP had lowest levels on day 1 after SAH and increased on days 2 to 4. Moreover, age, poor neurological status upon admission, cerebral infarction and peak hsTnT were independently associated with poor late outcome.

The area under the curve (AUC) for the first 4 days was used by Nyberg et al. (39) to quantitatively measure the BNP load during the first critical part of the disease in 138 patients with a SAH. A more severe SAH defined by a higher Fisher and World of Neurosurgical Societies grade, neurological deficits, an aneurysm, infections or higher levels of troponin I at admission had a larger AUC for NT-proBNP. Women, older people and those with poor outcomes also had larger AUC for NT-proBNP.

Terao et al. (40) investigated the relationship between urinary albumin/creatinine ratio (ACR), NT-proBNP level and neurological outcome after SAH in 61 patients. NT-proBNP highest levels were above normal limits in 93% patients, while 85% of them developed microalbuminuria. The study demonstrated on the one hand that the peak value of NT-proBNP was significantly associated with peak troponinI value and highest ACR. On the other hand, peak ACR and Hunt-Hess grade were independent predictors of poor neurological outcome.

Neurogenic myocardial stunning

Prunet et al (3)(41) evaluated cardiac glucose metabolism and myocardial perfusion and assessed the duration and reversibility of cardiac sympathetic impairment after SAH in 30 hemodynamically stable acute phase SAH patients, by using F-fluorodesoxyglucose positron emission tomography (^{18}F-FDGPET), ^{99m}Tc-tetrofosmin and ^{123}I-meta-iodobenzylguanidine (^{123}I-mIBG). 83% revealed initial impairment of cardiac glucose metabolism and the defect pattern could not be explained by a single coronary artery distribution, while 90% exhibited initial impairment of cardiac sympathetic innervation. All patients had normal myocardial perfusion and normal left ventricular systolic function. There was a concordance of ^{123}I-mIBG and ^{18}F-FDG uptake abnormalities, as well as a common temporal evolution, which suggests the close relationship between myocardial sympathetic function and glucose metabolism; yet neither of them produced left ventricular systolic or diastolic dysfunction in this group of patients (41).

In a group of 300 ash patients, Malik et al. (42) tried to determine the risk factors for the occurrence of neurogenic stress cardiomyopathy (NSC), which they defined as having at least one of the following: ECG changes (long OQ, T wave inversions), troponin level higher than 0.1 or decreased ejection fraction and wall motion abnormalities on the echocardiogram. After a multivariate analysis, they concluded that higher Hunt-Hess grade on admission, smoking, older age and lack of hypertension were the strongest predictors of NSC.

In a larger group of 715 SAH patients, Bihorac et al. (43), aimed to compare short- and long-term outcomes in patients with different patterns of regional left ventricular dysfunction (RLVD) as a manifestation of stress-induced cardiomyopathy

after SAH. 28% (200 patients) of these patients had an echocardiogram for clinical evidence of cardiac dysfunction, 30% of whom (59 patients) had RLVD. The observation was that the risk of death was significantly higher in patients who need an echocardiogram in the first place, regardless of the presence or absence of RLVD on that echocardiogram.

Conclusion

SAH should probably be the most feared type of stroke event among clinicians. On the one hand, it affects younger adults and individuals in their prime, therefore the individual disability burden and consequential social impact is devastating. On the other hand, SAH is a multisystem disease, and medical complications have been identified as factors that can contribute to worse outcomes, thereby awareness of this fact is warranted.

Cardiac abnormalities are common after SAH, even in non coronary-disease patients. Clinically significant arrhythmias after SAH are associated with a high mortality rate, as well as serious cardiac and neurological comorbidities[17]. These patients should be submitted to a close cardiac monitoring.

Some patients (20-30%) present with acute cardiac enzyme elevation, and an increase in troponin I, which occurs in more severe patients, correlates with poor long-term outcome. Increased levels of troponin, but also NT-proBNP, upon admission are both independently associated with delayed cerebral ischemia (11)(12). Troponin I and NT-proBNP elevation should therefore be early detected and closely monitored and those patients timely managed by a multidisciplinary team of doctors (44).

We should also bear in mind the fact that cardiac alterations associated with SAH include both systolic and diastolic dysfunction of the left ventricle, and that, in order to prevent pulmonary and other organ congestion due to heart dysfunction, it is strongly advised to perform echocardiography on admission of a SAH patient, and to repeatedly monitor this way a patient with SAH and RLVD during the triple H therapy (2)(14)(34)(36).

For comatose OHCA resuscitated patients, initial ED evaluation might be sufficient to differentiate between an ACS or a SAH as the cause of the cardiac arrest, prior to further, time consuming tests (22).

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