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RESEARCH ARTICLE

EXTRA-NEUROLOGICAL COMPLICATIONS OF SPONTANEOUS ARACHNOID HEMORRHAGE ABOUT 30 CASES

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ABSTRACT

Subarachnoid hemorrhage (SAH) is responsible of many neurological complications. However, other extra-neurological complications may occur involving the outcome of patients and worsening their prognosis. We report in this retrospective study 30 cases of subarachnoid hemorrhage that were hospitalized over a period of 3 years in our intensive care department A1 of Hassan II University Hospital, Fez, Morocco. The objective of our study is to evaluate the incidence of extra neurological complications of SAH, to describe their epidemiological and clinical characteristics to determine their impact on prognosis. Extra neurological complications were observed in 50% of cases. Metabolic complications (56.70%) were the most common followed by respiratory complications (43.3%) and cardiovascular complications (36.7%). The left heart failure, adult respiratory distress syndrome (ARDS) and renal failure were the most commonly reported. During our analysis, the factors predicting the occurrence of extra neurologic complications were: presence of headache on admission (p=0.03), grade WFNS > III (p=0.002), the depth of the initial Glasgow Coma Score (p=0.0001), modified Fisher score 4 (p=0.03), the presence of associated lesions on the initial scan (p=0.001), aneurysmal pathology (p=0.0001), the occurrence of complications neurological (p=0.033). The overall mortality was 30%. The results of our study concluded higher mortality in the group of patients with an extra-neurological complication. Therefore, the prevention and management of systemic complications are important for improving the overall clinical outcome after SAH.

INTRODUCTION

Subarachnoid haemorrhage (SAH) is an uncommon pathology; accounting for only 5% of all strokes (cerebrovascular accidents). Spontaneous rupture of intracranial aneurysms is involved in 85% of cases. SAH remains a worldwide leading cause of death and neurological disability. In fact, the mortality rate is approaching 50% and less than 60% of SAH survivors return to functional independence. Aside from the secondary neurological injury induced by this stroke subtype, SAH is also significantly associated with extra neurological complications. The related mechanisms include activation of the sympathetic nervous system, release of catecholamines and other hormones, and inflammatory responses. Indeed, extra neurological complications are significantly correlated to the severity of SAH-induced brain injury. The most frequent extra neurological complications occurring after SAH include pulmonary edema and pneumonia, cardiac arrhythmia, renal and hepatic dysfunction, electrolyte disturbance, and hematologic derangements. Indeed, these complications assume a prominent role in the overall outcome of SAH patients.

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The objective of our study is to determine the incidence of extra neurological complications of SAH, to describe their epidemiological and clinical characteristics and evaluate their impact on prognosis.

MATERIALS AND METHODS

Our work is a retrospective, descriptive and analytical study carried out over a period of 3 years (January 2016 - January 2019), including all cases of subarachnoid hemorrhage that have been hospitalized in the intensive care department A1 of Hassan II University Hospital, Fez, Morocco. All data was collected from the medical records, and supplemented by data from the computerized medical file, allowing the collection of the maximum data. Any SAH secondary to trauma was excluded from the study. The descriptive statistical study was carried out using the software SSPS (Statistical Package for the Social Sciences). The univariate analysis of the qualitative data consisted of the comparison of frequency between two qualitative variables and was performed using the $\chi 2$ test (two chi). The alpha risk threshold was set at 5%; however, a value of $p < 0.05$ was considered statistically significant.

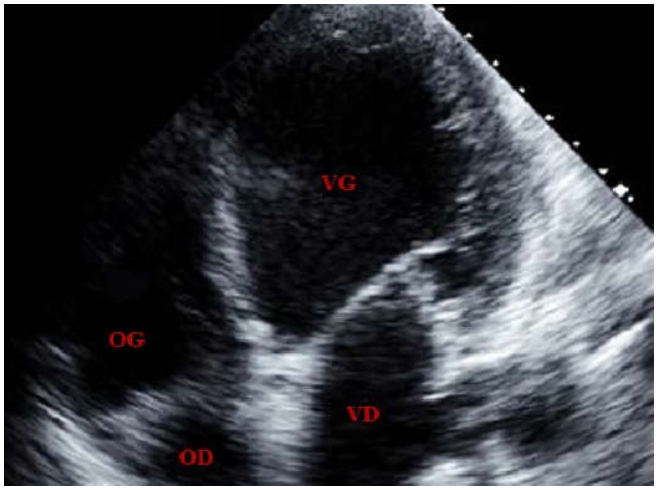

Fig 1. Tako-tsubo syndrome

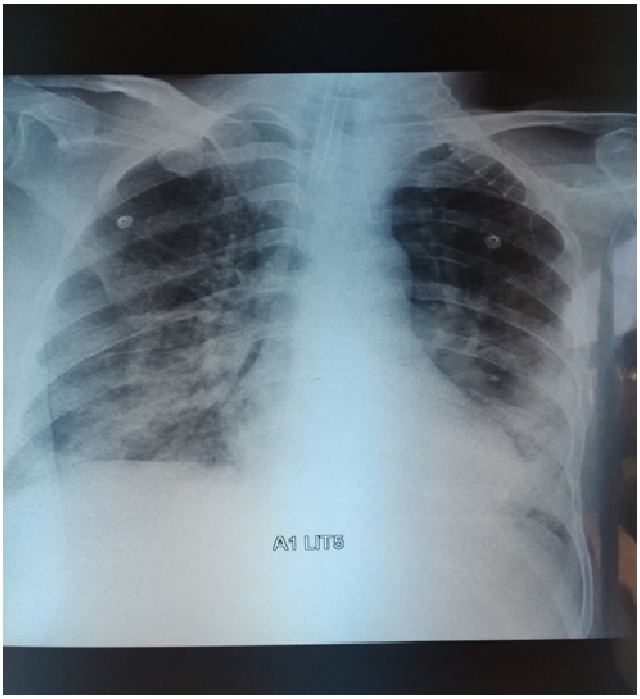

Fig. 2. Neurogenic pulmonary edema

RESULTS

We collected a total of 30 cases of subarachnoid hemorrhage. The overall incidence of extra neurological complications was 50%. Cardiovascular, respiratory and metabolic complications were the main ones with a frequency of 36.7%; 43.3% and 56.7% respectively. Hemostasis disorders were not very common (13.3%). Cardiovascular complications were represented by failure left cardiac present in 16.7%; stress cardiomyopathy (Tako-Tsubo cardiomyopathy) in 13.3% of patients and a cardiac arrest occurred in 10% of cases (n = 3). The elevation of Troponin was revealed in 20% of patients and modifications of the electrocardiogram (ECG) were noted in 16.7% of cases.The respiratory complications identified in our study were neurogenic acute pulmonary edema in 6.7% of cases; ventilator-associated pneumonia in 26.7%; Inhalation pneumonia in 13.3% of patients and acute respiratory distress (ARDS) in 33.3% of cases.

Metabolic complications were the most common complications in our series. They were mainly kidney failure in 46.7% of cases, one of whom had chronic renal insufficiency known from the moment of admission, which worsened during his stay; and a hypokalemia in 40% of cases. Hyponatremia and hyperglycemia were similarly objectified at 23.3 % of patients. Hypernatremia and hypomagnesemia had the same frequency of occurred in 20% of cases. Hemostasis disorders were represented by thrombocytopenia in 6.7% of patients and a low prothrombin (TP) in only 4 cases.Our statistical analysis, according to epidemiological and clinical data, could find statistically significant predictors for the occurrence of extra-neurological complications. Indeed, presence of headache on admission (p=0.03), grade WFNS > III (p=0.002), the depth of the initial Glasgow Coma Score (p=0.0001), modified Fisher score 4 (p=0.03), the presence of associated lesions on the initial scan (p=0.001), aneurysmal pathology (p=0.0001), the occurrence of neurological complications (p=0,033) especially intracranial hypertension (p=0.018) were significantly correlated with increased incidence of extra-neurological complications. The evolution of patients was favorable in 70% of cases in our series. The length of stay in the intensive care unit varied from 2 to 30 days; with a death rate reaching 30%. The results of our study concluded that mortality was higher in the group of patients presenting an extra-neurological complication than that presenting a neurological complication. Indeed, the mortality noted in group of patients who have had an extra-neurological complication is 56.3% of the cases compared to 43.7% for the rest of the patients.

DISCUSSION

Extra-neurological complications are directly related to the severity of brain lesions induced by SAH and indicate the clinical outcome in patients (Solenski *et al*., 1995). These complications range from disorders of sodium homeostasis to cardiac abnormalities. The main mechanism that can explain the occurrence of extra-neurological complication is a massive activation of the sympathetic nervous system leading to massive release of catecholamines (Naredi *et al*., 2000). This catecholaminergic "stress" can therefore be responsible for failures organs such as myocardial necrosis, pulmonary edema, hyperglycemia stress and dyskalemia (Legros, 2017). Systemic inflammatory response syndrome (SIRS), occurring with an incidence from 29% to 87% in SAH patients (Wartenberg *et al*., 2006; Gruber *et al*., 1999), is also reported to be responsible of extra cerebral organ dysfunction and acute lung injury (Legros *et al*., 2017). Cardiac complications after SAH are frequent and affect 25 to 100% of patients. It includes electrocardiographic (ECG) abnormalities, arrhythmias, myocardial infarction (both non-ST elevation and ST-elevation), left ventricular (LV) dysfunction, elevation of Troponin, and even cardiac arrest (Ahmadian, 2013; Franco, 2013). These complications are more common in severe forms of SAH (WFNS> 3), they are providers of a higher mortality; however, survivors, they do not worsen the long-term neurological prognosis (Legros, 2017). In our series, cardio-vascular complications accounted for 36.7% cases thus joining the data of the literature. In fact, 81% of patients had a WFNS score> 3; 87.5% of whom died during their stay in unit care thus reflecting the prognosis reserved for this category of patients.

The main biomarkers of the cardiac repercussions of SAH are the MB isoenzyme of creatine kinase (CK-MB), Cardiac troponin I and brain natriuretic peptide (BNP) (Hans *et al*., 2005). However, Cardiac troponin I (cTnI) has the advantage of being able to identify with high sensitivity and average specificity a myocardial lesion. Elevated serum levels of cTnI were observed in 20% of patients with SAH in patients with many cohorts (Tung *et al*., 2004; Parekh *et al*., 2000), as well as in our series. Previous studies have shown that 17 to 28% of SAH patients developed elevated serum levels of cTnI. In severely affected patients with elevated levels of cTnI, reduction of cardiac output may increase the risk of cerebral ischemia and poor outcome related to vasospasm (Deibert *et al*., 2003). A retrospective study including 617 consecutive SAH patients demonstrated that patients with high troponin levels demonstrated an increase in mortality (Hans *et al*., 2005). A variety of ECG changes, including T-wave inversions, ST depression, high R waves, prolongation of the corrected QT interval, and large U waves, have been frequently documented in SAH patients. The incidence of ECG abnormalities varies between 49 and 100% according to the authors (Sakr *et al*., 2002). This great variability is explained by the existence cardiac pathology in some patients, regardless of whether or not SAH. Indeed, in a prospective study involving 406 patients, alterations ECG were observed in 82% of cases with a higher incidence in patients with cardiovascular risk (Rudehill *et al*., 1987).

In addition, 35% of patients develop cardiac arrhythmias in the 2 weeks following aneurismal rupture with a frequency peak at the 2nd and 3rd day. Only 5% of these arrhythmias are severe and rarely fatal (Solenski *et al*., 1995). Unlike the literature, ECG changes were not very manifestos in our series. Indeed, we have objectified ECG modifications in 16.7% of cases. All these patients with ECG modification were severe with a WFNS score of 4 or 5. Myocardial infarction and cardiogenic shock may occur as a result of the initial bleeding accident. The rate of clinical cardiac decompensation is from 4 to 13% (Solenski *et al*., 1995; Mayer *et al*., 1999). At echocardiography, the incidence of dysfunction left ventricle (LV) is between 8 and 100% (8) depending on whether the patient has cardiac or not. This result is particularly relevant as 80% of these patients will present cardiogenic shock and where 60% of them will develop pulmonary edema (Szabo, 1993; Hans *et al*., 2005). The abnormalities of myocardial perfusion and contractility are not related to ECG abnormalities (Szabo *et al*., 1993) but the ventricular dysfunction is more common in patients in WFNS grade 4 or 5. As described in the literature, left heart failure was evidence clinically and echocardiographically in 16.7% of cases in our series, 80% of whom were severe SAH (WFNS> 3), 60% presented a cardiogenic shock and 40% developed a pulmonary edema. The evolution of this group of patients in our series was fatal. Only a patient with a WFNS score of 1 and presenting left heart failure had survived among this group. Tako-tsubo syndrome (Fig 1), a rare acquired stress cardiomyopathy characterized by LV dyskinesia and symptomatology typical of acute myocardial infarction, is also described in 1.2 to 26% of ultrasound studies during a SAH (Talahma *et al*., 2016). Although the pathogenesis of tako-tsubo syndrome has not yet been established, compelling literature supports the theory that acute cardiac sympathetic disruption accompanied with norepinephrine seethe and spillover are the mechanisms of tako-tsubo syndrome (Shams, 2012). There is probably a genetic predisposition. The female predominance is not explained, but hormone involvement sexual abuse seems likely (Legros *et al*., 2017). This entity represents 13.3% of the cases in our series, thus joining the data from other studies. 75% of the cases were women; and presented a serious SAH (WFNS> 3). Respiratory complications after an SAH are a set of lung dysfunctions, which include pneumonia, ARDS and neurogenic pulmonary edema (NPE) (Chen *et al*., 2014). Hypoxemia occurs in the acute stage of SAH. Indeed, oxygenation deficits were observed in 43% to 92% of patients with SAH, the most often due to pulmonary edema (Chen *et al*., 2014). Respiratory complications remain the leading cause of extra neurological mortality of SAH (Schuiling, 2015). This entity was present in 43.3% of patients in our series and burdened mortality of 61.5%. Pneumonia occurs in approximately 20% of patients as a result of SAH with an increased associated risk of mortality (Hall, 2017). They are frequent; secondary to the alteration of the level of consciousness may promote micro inhalation, or massive inhalation (Legros *et al*., 2017). Ventilator-associated pneumonia (VAP) is present in about 50% of patients and is mainly due to Staphylococcus aureus sensitive to methicillin (Cinotti *et al*., 2014).

The most common cause is infection, which is already a recognized complication of aneurysmal subarachnoid hemorrhage (Hall, 2017). However, immunosuppression induced by SAH may increases the risk of pneumonia, especially in high grade WFNS in which she persists beyond the 3rd day after hemorrhage. Independent risk factors for the development of pneumonia in case of SAH include: Age > 65 years, male sex, severity of SAH, pulmonary hypertension and edema cardiogenic pulmonary (Chen *et al*., 2014). In our series, the most common complication was represented by the pneumonia (40%), including a nosocomial VAP (26.7%) and Inhalation pneumonitis (13.3%). This incidence of pneumonia is greater at rates reported by previous studies (Solenski *et al*., 1995; Claudio Cavallo *et al*., 2018). Indeed, this group of patients mainly contains subjects over 65 years of age (61.5%), male (61.5%) and 84.6% of patients with high grade WFNS, with an average duration of intubation of 7 days. All these factors contributed to the poor prognosis of this group of patients who has a mortality rate of 61.5%. Acute respiratory distress syndrome (ARDS) is a complication affecting less than 20% of hospitalized patients with aneurysmal SAH, mainly of pulmonary origin (inhalation, ...), with an important impact on mortality (Legros *et al*., 2017; Veeravagu *et al*., 2014). Predictors of the occurrence of ARDS reported in several studies were age, severity of neurological involvement, a significant volume of SAH in tomography (Fisher grade), hypoproteinemia and hyperglycemia admission (Solenski *et al*., 1995; Claudio Cavallo *et al*., 2018; Veeravagu *et al*., 2014). Our series reported a higher rate of ARDS than the literature (33.3%); 60% of whom were> 65 years old. All cases of ARDS identified in our series had a Fisher score modified to 4. Mortality has reached 60% of cases in this group of patients. Neurogenic pulmonary edema (NPE) (Fig 2) is a common complication of severe SAH (18). More than 20% of patients are subject to it, unlike our series, where this entity was only in 6.7% of the cases of SAH. NPE is usually suspected when there are no underlying lung diseases, and NPE is found in 23% to 71% patients during hospitalization (Solenski *et al*.,

1995). SAH patients with NPE were usually younger and died sooner than those without. The development of pulmonary edema most frequently occurs within the first week from the beginning of the SAH with a peak around 3rd day. The incidence of NPE decreased with time after SAH. Renal failure was associated with volume loading and the aggressive maintenance of mean arterial pressure. In addition, SAH-induced sympathetic activation may play a crucial role in progression of renal failure (Grassi, 2011). SAH patients frequently receive antibiotic therapy and undergo a significant number of contrast radiographic studies, which have been closely associated with renal dysfunction. In a retrospective analysis of a series of 787 SAH patients, a seemingly insignificant decrease in kidney function can adversely affect the 3-month outcome independently of other known predictors (Zacharia, 2009). Renal dysfunction was reported in 0.8% to 7% of patients with SAH (Solenski *et al*., 1995). These data remain much lower than those found in our series. Indeed, kidney failure was objectified in 46.7% of our patients. Hyponatremia is a relatively common complication of SAH aneurysms, its main cause is the cerebral salt loss syndrome (CSWS) and more rarely the secretion syndrome inappropriate ADH (SIADH). It seems extremely important in front of the presence of hyponatremia in a context of HSA to recognize the syndrome responsible for setting up the appropriate treatment (Legros *et al*., 2017).

Hypernatremia is rarer, secondary most often to diabetes insipidus of central origin reflecting post-pituitary or hypothalamic pain (Legros *et al*., 2017). In many studies, hyponatremia is diagnosed in about 30% of patients with SAH (Kurokawa *et al*., 1996). In more recent series, hyponatremia is only found in 14% of patients (Sayama *et al*., 2000). Thus, the incidence of hyponatremia ranges from 10 to 34% in patients with HSA, which aggravates their prognosis (Chen *et al*., 2014). In a recent series of 298 patients, if hyponatremia was noted in 30% of patients, 19% of them had hypernatremia. While the occurrence of hyponatremia did not change the prognosis, that of a hypernatremia, appearing in the first four days, was significantly associated with an unfavorable neurological evolution (Qureshi, 2002). Our results are in good agreement with the literature data. Indeed, the Hyponatremia rate in our series was 23.3%. Hypernatremia was present in 20% of cases. Hypokalemia has been detected in about 50% of all patients with SAH (Fukui *et al*., 2003). A recent study seems to show that hypokalemia at admission would be a pejorative evolution factor associated with hypomagnesemia (Legros *et al*., 2017). In our series, we report a rate of hypokalemia close to literature with a frequency of 40%. The presence of hypomagnesemia is just as common and seems quite good correlated with the volume of blood present in the subarachnoid spaces (Legros *et al*., 2017). Hypomagnesemia is present in 38% of cases after SAH and is associated with a severity of SAH according to the Bergh study (van den Bergh, 2003). Hypomagnesemia occurred between the 2nd and 12th day after an SAH predicts the occurrence of delayed cerebral ischemia (Chen, 2014). However, a recent study did not recommend systematic administration of magnesium, since it could not improve overall clinical outcome after SAH (Legros, 2017). In our study, only 20% of patients had hypomagnesaemia, whose two-thirds (66.7%) had severe SAH with high initial WFNS.

This entity was underdiagnosed in our study as it is a measure which is not systematically performed in any patient admitted for SAH. Stress hyperglycemia is present at admission in 70 to 90% of all SAH patients (Ghosh *et al*., 2012). Its mechanism is sympathetic activation secondary to stress catecholaminergic, hepatic and pancreatic stimulating the production of glucagon and inhibiting insulin synthesis. The glucose level at admission is related to the severity of initial hemorrhage (Feng *et al*., 2012). Previous studies revealed that the initial hyperglycemia was an independent predictor of the occurrence of delayed cerebral ischemia and poor outcome in SAH patients. In our studies, hyperglycemia was present in 23.3 % of cases. Hemostasis disorders were represented in our studies by thrombocytopenia in 6.7% of patients and a low prothrombin (TP) in only 4 cases. In current literature, a high incidence of coagulative and fibrinolytic disorders was observed in patients with SAH, which was also associated with outcome. A prospective study showed high level of plasmatic thrombin/ antithrombin complex parallels clinical outcome (Nina, 2001). Predictors of occurrence of extra-neurological complications rarely reported in the literature. These complications are more common in severe forms of SAH (WFNS > 3) (Solenski *et al*., 1995). Some authors have reported factors that play a role in development of pneumonia in patients following SAH, in addition to already established risk factors, including mechanical ventilation and micro inhalation. Others found that age, initial neurological status (GCS), WFNS grade and Fisher score seem to have an impact on the occurrence of extra-neurological complications in patients with SAH, as well as prognosis and outcome neurological.

Conclusion

SAH is not only affecting brain tissue, but also impairing extra cerebral organs. Extra cerebral complications are associated with the high mortality rates and neurological impairments following SAH, even after adjustment for the severity of the initial neurological injury. Therefore, the prevention and management of extra neurologic complications is important for the improvement of the overall clinical outcome after SAH.

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