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IMPACT OF BIOCHEMICAL AND PSYCHOLOGICAL MARKERS OF STRESS ON OUTCOME OF SUBARACHNOID HAEMORRHAGE PATIENTS: A PROSPECTIVE STUDY.

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ABSTRACT **Observations & Results:** A total of 156 patients were included. Mean age being 50 years for spontaneous SAH and 35 years for traumatic SAH. Median GCS was 15 amongst 71.2% with aSAH compared to 62.9% with tSAH, while no patient with a SAH had GCS<9, 9.28% cases with tSAH had GCS<9 (p value=0.029). Neurodeficit was seen in 16.95% of aSAH compared to only 8.25% in tSAH (p value=0.01).WFNS grade 4 was seen in 1.69% of aSAH cases compared to 15.46% of tSAH (p=0.03). Type D personality was seen in 44.45% of aSAH patients compared to 38.46% of tSAH patients (p=0.1). PSLES evaluation showed severe stress in 21.05% of aSAH cases compared to 25.27% of tSAH cases (p=0.029). Serum cortisol levels were significantly higher in patients with SAH compared to matched controls (median [IQR]:36.0[23.7- 39.3]vs.14.0 [9.8-17.6] µmol/L, p value < 0.001), whereas serum CRP levels in SAH had statistically non-significant higher range (median [IQR]: 2.1 [1.0-6.2] vs. 2.2 [0.8- 4.4] mg/L, p value = 0.23). Microalbuminuria was significantly higher in patients with delayed neurological deficits (p = 0.026) and lower triglyceride levels were significantly associated with higher risk of vasospasm (p =0.004). Death was seen in a total of 11 aSAH patients and 28 tSAH cases. No significant difference was seen in mortality amongst the two groups with a compiled mortality of 39 patients (p = 0.614).
Conclusion: Stress and inflammation play key role in SAH and its outcome. To ensure safe outcome of patients, biochemical stress and inflammation need to be adequately controlled.

KEYWORDS : SAH; stress; aneurysm

INTRODUCTION: Subarachnoid hemorrhage is a pathological condition resulting from blood in the subarachnoid space,accounting for 5% of all strokes and aneurysm being the most common cause of spontaneous SAH.

TRAUMATIC SUBARACHNOID HEMORRHAGE (tSAH) frequently occurs following head injury.

Traumatic subarachnoid hemorrhage (tSAH) is caused by bleeding of cortical arteries, veins, and capillaries from brain surface. Rarely, tSAH can be caused by rupture of bridging veins or traumatic aneurysms [1].

Over the last 10 years, an increasing number of studies have focused on the role of tSAH in the outcomes of patients with TBI and information is now available from clinical studies, databases, and multicenter clinical trials of neuroprotective drugs. Authors of these studies found a higher incidence of unfavorable outcome (severe disability, persistent vegetative state, and death) in patients with tSAH than in those without such lesions. These analyses agree that tSAH is one of the most important independent prognostic factors for patient outcome [2,3,4,5,6].

The present study has been planned with an aim to evaluate various factors and their effect on the outcome in SAH patients. In our study we will focus on the biochemical and psychological stress markers.

AIMS & OBJECTIVES:

(1) To evaluate stress and type-D personality among patients presenting with SAH,
(2) To assess biochemical markers of stress in these patients,
(3) To analyze these parameters in context with neurological outcome.

MATERIALS & METHODS:

The current prospective study was carried out in the Department of Neurosurgery, at BANGUR INSTITUTE OF NEUROSCIENCES & SSKM HOSPITAL, IPGME & R, Kolkata, India, from 2015 – 2018. A total of 156 patients were enrolled. All patients were evaluated using PSLES & DS14 scales to analyze personality. Serum was obtained from all patients to study levels of CRP, Albumin, Cholesterol and Cortisol. GCS was noted at time of admission and SAH graded based on WFNS system.

Neurological deterioration if any were noted during the course of hospital stay. Mortality was noted amongst the study group. Neuropsychological evaluation was done within 24 hours of admission. DS 14 questionnaire was used only amongst conscious patients while PSLES was useful for both conscious as well as unconscious patients. All biochemical profiles were sent at 8 am the next day of hemorrhage to ensure true cortisol values could be obtained.

OBSERVATIONS & RESULTS:

Table 1: Mean Age distribution:Spontaneous SAH 50 yrs Traumatic SAH 35 yrs Table 2: gcs distribution:GCS Spontaneous SAH Traumatic SAH 15 42 (71.2%) 61 (62.9%)
12-14 14 (23.72%) 17 (17.52%)
9-11 3 (5.08%) 10 (10.31%)
<9 - 9 (9.28%)

At admission, median GCS was 15. 71.2% of spontaneous and 62.9 % of traumatic SAH patients had GCS

15/15. 23.72% (spont.) and 17.52% (traumatic) patients had GCS of 12-14/15, 5.08% (spont.) and 10.31%

(traumatic) had GCS of 9-11/15 and 9.28% of traumatic had GCS less than 9/15. Table 3: deficits at admission:Focal deficits Spontaneous SAH Traumatic SAH Absent 49 (83.05%) 89 (91.75%)

Present 10 (16.95%) 8 (8.25%)

16.95% (spont.) and 8.25% (traumatic) patients presented with neurological deficits.

Table 4: WFNS grading:Spontaneous SAH Traumatic SAH Grade 1 40 (67.8%) 45 (46.39%)
Grade 2 12 (20.33%) 20 (20.62%)
Grade 3 5 (8.47%) 17 (17.52%)
Grade 4 1 (1.69%) 15 (15.46%)

Table 5: type D personality (n=136):Spontaneous SAH (n=54) Traumatic SAH (n=78) No 30 (55.55%) 48 (61.54%)

Yes 24 (44.45%) 30 (38.46%)

Table 6: PSLES (n=148): Spontaneous SAH (n=57) Traumatic SAH (n=91) 1 (mild) 18 (31.58%) 30 (32.97%)
2 (moderate) 27 (47.37%) 38 (41.76%)
3 (severe) 12 (21.05%) 23 (25.27%)

Various biochemical markers were used- TLC with mean value 9100 and 11000 respectively, serum albumin- 4.1 and 3.5, lipid profile including serum cholesterol –145 and 162, serum triglycerides- 155.0 and 161.3, VLDL- 33.96 and 37.23, serum cortisol 29 and 43 and C-reactive protein was found to be positive in 42.37% and 60.82% of patients as tabulated below.

NO YES
Number Of Cases TYPE D PERSONALITY
TYPE D PERSONALITY AND SAH
Spontaneous SAH Traumatic SAH

MILD MODERATE SEVERENumber Of Cases PSLES
PSLES & SAH
Spontaneous SAH Traumatic SAH

Table 7: Biochemical markers:
Spontaneous SAH Traumatic SAH Total leucocyte count 9100 11000
Albumin 4.1 3.5
Cholesterol 145 162
Triglycerides 155.0 161.3
VLDL 33.96 37.23
Cortisol 29 43
CRP positive 25 (42.37%) 59 (60.82%)
CRP negative 33 (55.93%) 38 (39.17%)

Serum cortisol levels were significantly higher in patients with SAH compared to matched controls (median [IQR]: 36.0 [23.7-39.3] vs. 14.0 [9.8-17.6] μmol/L, p value < 0.001), whereas serum CRP levels in SAH had statistically non-significant higher range (median [IQR]: 2.1 [1.0-6.2] vs. 2.2 [0.8-4.4] mg/L, p value = 0.23).

Table 8: serum total cortisol level in patients suffered from DIND (mean value):
Delayed ischemic neurological deficit was assessed in patients with sub-arachnoid hemorrhage and serum cortisol levels were assessed in these cases. Patients who suffered from DIND had higher total cortisol levels, which was found to be statistically significant (p=0.011).

TLC ALBUMINCHOLESTEROTRLIGLYCERIDE VLDL CORTISOLCRP POSITIVCERP NEGATIVE
Mean Value In Standard units BIOCHEMICAL MARKER
BIOCHEMICAL STRESS PROFILE IN SAH
Spontaneous SAH Traumatic SAH
Nature of SAH Mean Cortisol Value (μmol/L)

{Normal range = 5 to 23 μmol/L} Spontaneous SAH post-operative 27.62 Traumatic SAH 39.45

The outcome was assessed in these patients using Glasgow outcome scale. The median GOS at discharge

was 4(3-5) and 3 months was 5(4-5). There was significant correlation between plasma cortisol levels and GOS within first few weeks of admission in both groups (Spearman ρ = 0.36, p value = 0.002).Table 9: GOS in spontaneous SAH: 1 month (n=59) 3 months (n=40)
5 16 30
4 30 5
3 4 2
2 1 -
1 8 3

GRADE 5 GRADE 4 GRADE 3 GRADE 2 GRADE 1

Number Of Cases GOS GLASGOW OUTCOME SCALE IN SPONTANEOUS SAH
1 MONTH 3 MONTHS Table 10: GOS in traumatic SAH: 1 month (n=97) 3 months (n=54)
5 24 35
4 50 15
3 3 32 2 1
1 18 10
Table 11 GOS Median(IQR)
At discharge 4 (3-4)
At 3 months 5 (4-5)

GRADE 5 GRADE 4 GRADE 3 GRADE 2 GRADE 1
Number of Cases GLASGOW OUTCOME SCALE GLASGOW OUTCOME SCALE & TRAUMATIC SAH
1 MONTH 3 MONTHS
Table 12: Deaths:
Spontaneous SAH Traumatic SAH
Death at 1 month 8 (13.56%) 18 (18.56%)
Death > 1 month 3 (5.08%) 10 (10.31%)

In the current study, comparison of all the parameters was done with vasospasm. Triglycerides, VLDL, and serum albumin have significant influence on vasospasm. With decreasing serum albumin, there is a significant increase in the incidence of delayed neurological deficits (p -0.029). The incidence of vasospasm significantly increased with decreasing TG (p-0.004) and decreasing VLDL (p-0.005).

It was also found that PSLES scale is significantly correlating with vasospasm, i.e., with increasing stress there is an increasing incidence of vasospasm in aneurysm patients with p value- 0.015.

Development of vasospasm and delayed ischemic neurological deficit had an impact on Glasgow outcome scale. Development of vasospasm has a p value of 0.008, suggesting with the development of vasospasm there was a worsening GOS. Development of new infarct led to a worsening of GOS (p-0.001).

DISCUSSION:
In our study, we have studied the various parameters of psychological and biochemical stress markers and the impact on outcome in subarachnoid hemorrhage patients. Stress is found to be associated with many diseases and has an impact on clinical outcome in these diseases. Stress is defined as the perception of excessive threats or exists as a distinct entity and can undergo sudden provoked or unprovokedworsening, causing acute stroke. Chronic dysfunctional response to stress can include migraine, hypertension and systemic platelet activation leading to a hypercoagulable state [7].

We studied the role of type D personality using DS-14 scale and PSLES scores. There are many studies which have shown the role of type D personality in cardiovascular diseases and its outcome.

Type D was associated with poor physical and mental health status and poor self-management of the disease. Type D is a vulnerability factor that not only affects people with cardiovascular conditions but also those with other medical conditions. Studies on Type D among cardiovascular patients have shown that Type D is an independent predictor of negative outcomes such as poor health status, recurrent myocardial infarction and increased risk of mortality [8,9].

There is no study which has demonstrated the role of type D personality in outcomes of SAH patients. In our study although 34.61% of the patients had type D personality, there was no significant difference in clinical outcomes among the patients of SAH with or without type D personality. PRESUMPTIVE STRESSFUL LIFE EVENTS SCALE (PSLES) is a similar scale for evaluating stress particularly suitable for Indian population. The role of stressful life events in the etiology of various diseases has been a fertile field of research for the last twenty-five years. A host of studies have suggested a positive relationship between stressful life events and subsequent illness [10,11]. A similar though less consistent relationship between the onset of psychiatric illness and life events has also been reported.

PSLES has not been studied in the clinical outcome in SAH patients before. In our study, there is an increasing incidence of vasospasm with increasing stress.

We have tested various blood markers in our patients and studied the role of these markers in outcome of the patients. We have used total leucocyte count, serum cortisol, serum CRP, serum albumin, serum cholesterol, triglycerides and VLDL as markers.

CRP measurement, as the most accepted and utilized inflammation marker, was included in the Randox UK-s stroke-diagnostic neuro-panel. As this biochip-controlled test was originally designed to

diagnose ischemic stroke, it included the high sensitivity CRP (hsCRP) assay version with a dynamic range of 0-15mg/L. Frontera et al. (2012) concurred showing that CRP blood levels were significantly higher in poorer grade patients over time and correlated with severity of SAH on admission [12]. Jeon et al. (2012)

demonstrated specifically in surgical SAH patients, that pre-operative and post-operative blood levels of CRP were associated with poor outcome [13]. Recently in 2015, Ludvig et al of Gothenburg found that CRP levels were better predictors of outcome in SAH patients as compared to Fischer grading and WFNS grading. In our study, though 70 (44.87%) patients were positive for CRP levels there was no significant impact on outcome in terms of vasospasm and GOS.

Microalbuminuria is a product of metabolism and a biomarker of infection and sepsis. Terao et al. (2007) found a microalbumin/ creatinine ratio greater than 200 mg/g to be a potent independent predictor of unfavorable neurological outcome [14]. Although non-specific, this biomarker has potential as it has successfully been utilized in other inflammatory disease states. In our study, we have studied the role of serum albumin and its impact on outcome. The mean serum albumin was 4.1 in non-traumatic and 3.5 in traumatic SAH patients. With decreasing serum albumin, there is an increase in the incidence of delayed neurological deficits. (p-0.029).

In a large cohort study (three city study in France) of elderly men and women, low triglycerides levels were associated with an increased risk of hemorrhagic stroke and a decreased risk of ischemic vascular events.

The association between triglycerides and hemorrhagic stroke was particularly strong in men, in subjects with high blood pressure and in those with low cholesterol levels. A low level of triglycerides (serum triglycerides ≤0.94 mmol/L) was associated with a more than twofold increased risk of hemorrhagic stroke in both simple and fully adjusted models [15]. The mechanisms explaining how low triglycerides could promote hemorrhagic stroke in the elderly remain unclear.

In our study, we found a significant correlation between low triglycerides and vasospasm (p- 0.004), and with decreasing VLDL and vasospasm (p-0.005). The hypothesis we propose is that lower TG and VLDL can cause endothelial dysfunction which can lead to vasospasm.There is an evidence showing that the cortisol dynamics might be associated with the severity and outcome after subarachnoid hemorrhage [16]. Although a previous study on the pituitary adrenal function in acute subarachnoid hemorrhage (SAH) has shown that the SAH severity does not affect cortisol concentration, that study did not describe the relationship between the total cortisol level and the patient's neurologic state [17]. Also, they were unable to show any difference in the adrenal response between comatose (GCS<8) and non-comatose patients.

Vergouwen et al. have shown that the increase cortisol level is associated with the DIND, through hyperglycemia and endothelium dysfunction (von Wille brand factor) [18]. Whether the cortisol is just part of the stress process and is unrelated to the ongoing worsening of patient neurologic status, or it is contributing to make the patient worst, is still unclear.

Our study supports the evidence that the total morning cortisol level in serum is associated with the onset of DIND. Although higher values of total serum cortisol were found in traumatic SAH group but the difference was not statistically significant. Similar result was also shown by Julius et al in 2011.

The evidence suggests to consider the total cortisol level as one of the factors before releasing the patient from ICU care or NSU to the ordinary ward. During the first few days of SAH, the cortisol level is totally dependent on the Hypothalamo - Pituitaryadrenal (HPA) function. The ACTH is released from the anterior pituitary to stimulate cortisol release from the adrenal gland. It is the major source of the cortisol, but on POD 7, the function is taken over by the extra ACTH cortisol release. In the second week, although the ACTH level is decreasing, the total cortisol levels were persistently high. It supports the evidence that there is an extra ACTH cortisol release.

Interleukin 6 (IL-6) constitutes a potentially important factor of extra-ACTH cortisol release84, besides IL- 1 and tumor necrosis factor-alpha85.

The role of inflammatory pathway becomes substantial in the second week. There are various studies on GOS and clinical outcome in SAH. A retrospective study of 56 patients withSAH who were assessed for outcome at 6 months using the GOS, found that the worst grade recorded on the WFNS Scale or GCS before surgery closely correlated with outcome [19]. In our study development of vasospasm and new infarct had an impact on Glasgow outcome scale at 3 months.

CONCLUSION:

With such a variable and tremulous course amongst patients with SAH; our study offers insight into important variables that hold the key to facilitate improved survival with a significant reduction in morbidity associated with SAH. The association of PSLES with vasospasm was found to be significant (p = 0.029). Amongst the various available biomarkers, Low cholesterol (p = 0.004) and High cortisol (p = <0.001) were associated with increased incidence of vasospasm and thus increased the Late onset neuro deficit amongst the patients.

A detailed evaluation is still required in patients being admitted to a critical care unit for SAH.

All possible measures have to be taken to reduce morbidity and mortality amongst individuals with sub – arachnoid hemorrhage.

REFERENCES

(1) Freytag E. Autopsy findings in head injuries from blunt forces. Statistical evaluation of 1,367 cases. Arch Pathol. 1963;75:402-13.
(2) Kakarieka A, Schakel EH, Fritze J. Clinical experiences with nimodipine in cerebral ischemia. J Neural transmission Supplementum. 1994;43:13-21.
(3) Eisenberg HM, Gary HE, Aldrich EF, Saydjari C, Turner B, Foulkes MA, et al. Initial CT findings in 753 patients with severe head injury. A report from the NIH Traumatic Coma Data Bank. J Neurosurg. 1990;73:688-98.
(4) Morris GF. A new, practical classification of traumatic subarachnoid hemorrhage. Acta Neurochir Suppl. 1997;71:382.
(5) Lang DA, Teasdale GM, Macpherson P, Lawrence A. Diffuse brain swelling after head injury: more often malignant in adults than children? J Neurosurg. 1994;80:675-80.
(6) Selladurai BM, Jayakumar R, Tan YY, Low HC. Outcome prediction in early management of severe head injury: an experience in Malaysia. British J Neurosurg. 1992;6:549-57.
(7) A.E. Eggers et al, A chronic dysfunctional stress response can cause stroke by stimulating platelet activation, migraine, and hypertension, Medical Hypotheses (2005) 65, 542–545
(8) Denollet J, Sys SU, Stroobant N, Rombouts H, Gillebert TC, Brutsaert DL. Personality as independent predictor of long-term mortality in patients with coronary heart disease. Lancet 1996;347(8999):417–21.
(9) Denollet J, Vaes J, Brutsaert DL. Inadequate response to treatment in coronary heart disease: adverse effects of Type D personality and younger age on 5-year prognosis and quality of life. Circulation 2000;102(6):630–5.
(10) HOWIES, T. H. AND R>HE, R. H. (1967). The Social Readjustment Rating Scale. J. Psyr.hosom. Res., 11, 213.
(11) Wow, H. G. (1950). Life Stren and bodily diseases, Formulation association for research in Neurosis and Mental disease. Proceedings 29, 1059.
(12) Frontera JA, Aledort L, Gordon E, et al. (2012). Early platelet activation, inflammation and acute brain injury after a subarachnoid hemorrhage: a pilot study. J Thromb Haemost 10:711–13.
(13) Jeon YT, Lee JH, Lee H, et al. (2012). The postoperative C-reactive protein level can be a useful prognostic factor for poor outcome and symptomatic vasospasm in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg Anesthesiol 24:317–24.
(14) Terao Y, Takada M, Tanabe T, et al. (2007). Microalbuminuria is a prognostic predictor in aneurysmal subarachnoid hemorrhage. Intensive Care Med 33:1000–6.
(15) Audrey bon adventure et al, Triglycerides and risk of hemorrhagic stroke vs. ischemic vascular events: The Three-City Study; Atherosclerosis 210 (2010) 243–248
(16) Poll EM, Bostrom A, Burgel U, Reinges M, Hans FJ, Gilsbach JM, et al. Cortisol dynamics in the acute phase of aneurysmal subarachnoid hemorrhage: Associated with disease severity and outcome. J Neurotrauma. 2010;27:189–95.
(17) Bendel S, Koivisto T, Ruokonen E, Rinne J, Romppanen J, Vauhkonen I, et al. Pituitary-Adrenal function in patients with acute subarachnoid haemorrhage; A prospective cohort study. Crit Care. 2008;12:R126
(18) Vergouwen MD, van Geloven N, de Haan RJ, Kruyt ND, Vermeulen M, Roos YB. Increased cortisol levels are associated with delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2010;12:342–5.
(19) Chiang VL, Claus EB, Awad IA. Toward more rational prediction of outcome in patients with high grade sub arachnoid hemorrhage. Neurosurgery 2000;46:28–35.