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Management of severe subarachnoid hemorrhage; significance of assessment of both neurological and systemic insults at acute stage

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Summary

In order to elucidate mutual interrelationship between neurological and systemic dysfunctions in patients with subarachnoid hemorrhage (SAH) at acute stage, neurological condition, systemic complications and plasma catecholamine (CA) level were studied in 1431 consecutive cases admitted within 72 hours after the onset. Five hundred and twenty-four cases with Glasgow Coma Scale (GCS) score 8 or less were assigned to the group of severely ill cases (G-ill), 907 cases with GCS score 9 or more to that of the less ill group (G-well). Plasma CA level was extremely high at super-acute stage within an hour after bleeding and lowered fairly quickly within 24 hours to the normal range. Assuming the value obtained from a formula of [blood sugar level (mg/dl)/serum potassium concentration (mEq/L)] as stress index (SI), SI correlates well ($r = 0.4 \sim 0.6$) with serum catecholamine level at acute stage. Thus, sympathetic hyperactivity after SAH can be grossly estimated with SI. SI over 40 means that patients might have considerable neurological insults as well as systemic ones. For patients in G-well, SI over 50 means that there may be risks for systemic complications even in cases with good neurological condition.

Keywords: Subarachnoid hemorrhage; systemic complication; neurological grade; sympathetic storm.

Introduction

It is well known that patients with severe SAH are in severely ill condition not only by neurological but also by systemic insults. Systemic dysfunctions accompanying acute SAH are thought to be caused mainly by sympathetic hyperactivity which occurs at the onset of hemorrhage. Massive release of catecholamines (CA) by this abnormal sympathotonia often brings about life-threatening cardiopulmonary and systemic complications like varying types of arrhythmia, cardiac failure, neurogenic pulmonary edema (NPE) and/or extreme hypokalemia [1–8]. Clinical manifestation of neurological insults and that of systemic dysfunctions in patients with poor grade SAH have been studied well but separately so far. Thus, a precise relationship between these two clinical aspects of acute SAH have not yet been elucidated sufficiently [8]. In this paper, we describe the results of a study about relationship between these two conditions that are seemingly independent but actually connected well to each other.

Patients and methods

The cohort which was studied in this report comprised 1431 consecutive SAH patients admitted within 72 hours after the onset. Five hundred and twenty-four patients with Glasgow Coma Scale (GCS) score 8 or less on admission were studied as a severely ill group (G-ill), and 907 patients with GCS 9 or more were used as non-severely ill control (G-well). Blood sample for serum level of CA, potassium (K^+) or glucose (BS) was obtained at the emergency room immediately after patient's admission. Cases who had history of laboring renal insufficiency or diabetus mellitus and who underwent resuscitation for cardiopulmonary arrest caused by SAH were omitted from the cohort in order to exclude influences of these conditions on serum K^+ or BS level. Statistical analyses were made by Fisher's t-test, χ-square test or Kruskal-Wallis test. Regarding demographic background of the two groups, male to female ratio is 0.76 in G-ill and 0.64 in G-well that are not significantly different, while the average age is higher in the former group than in the latter (56.8 ± 13.1 vs 54.3 ± 12.0; $P < 0.01$).

Results

Serum CA level

Serum epinephrine level on admission in acute SAH patients is extremely elevated nearly up to the level of 800 pg/ml (almost 8–10 times higher than normal) immediately after the hemorrhage and then gradually falls down to the normal range within 24 hours. The spiky rising and rapid dropping of temporal profile

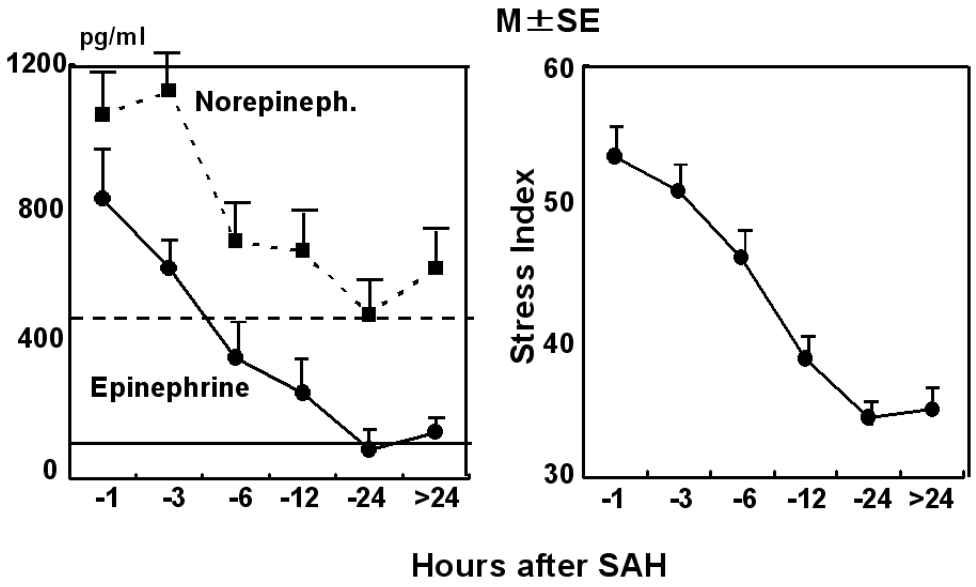

Fig. 1. *Left:* Time course of plasma CA after SAH. Dotted lines represent noradrenaline, and solid ones adrenaline. Horizontal lines are the upper normal limits. *Right:* Time course of SI. Note the identical pattern of CA level and SI

is almost the same as with serum norepinephrine levelin of which the initial peak value is around 1000–1200 pg/ml (3–4 times higher than normal) (Fig. 1, graph on the left).

Blood sugar, serum potassium level and stress index

An elevation of BS and reduction of K^+ are phenomena well-known to physicians treating patients suffering acute SAH. Serum level of these two substances correlate well to the neurological grade on admission with statistical significance ($P < 0.01$), that is mean BS level is higher and K^+ level is lower in the group of poorer grading. Consequently, providing a value calculated from BS level divided by serum potassium level ($BS^{mg/dl}/K^{+mEq/l}$) as Stress Index (SI), SI significantly correlates ($P < 0.01$) with clinical grade. Plotting a temporal profile of mean SI values at each time stage after SAH, time course of SI is almost identical with that of plasma CA (Fig. 1, graph on the right). A correlation coefficient between SI and catecholamines at each time interval from the onset of SAH is 0.5 to 0.6 with statistically significant probability ($P < 0.05$) at least up to 12 to 24 hours. Thus, one can roughly estimate the extent of sympathetic tone of patients with acute SAH in emergency rooms by using SI, which can easily be computed in ordinary clinical setting from serum BS and potassium level.

Comparing the composition of neurological grades in groups of every 5 SI scores, a significant difference is present between the groups with SI below and above 40 (Fig. 2, graph on the top). This means that groups with SI higher than 40 are significantly worse regarding neurological state than those with SI below 40 ($P < 0.01$).

Cardiopulmonary complications and SI

As manifestation of serious cardiopulmonary complications, neurogenic pulmonary edema (NPE) was observed in 14.6% of overall cases, apnea attack in 10.9%, cardiac failure in 2.6% and ventricular tachycardia or fibrillation (VT/VF) in 1.8%. Furthermore, ischemic ST/T changes on ECG were identified in 33.6%. These complications are more frequently observed in patients with higher SI, incidence of which is significantly different ($P < 0.05$) between the groups with SI below and above 40, and that with SI below or above 50 (Fig. 2, graph at bottom). Incidence of complications is 35.6% in G-ill and 12.5% in G-well with a significant difference ($P < 0.01$). Mean SI of G-ill is 58.0 ± 21.3 and that of G-well is 44.2 ± 16.4, which is significantly different ($P < 0.01$: Fig. 3, left columns). In G-ill, mean SI is 57.2 in cases with complications and 59.8 in those without (Fig. 3, columns in the mid), while in G-well, mean SI is significantly different ($P < 0.01$) in those with complications ($SI = 52.5$) and those without ($SI = 41.9$) (Fig. 3, right columns).

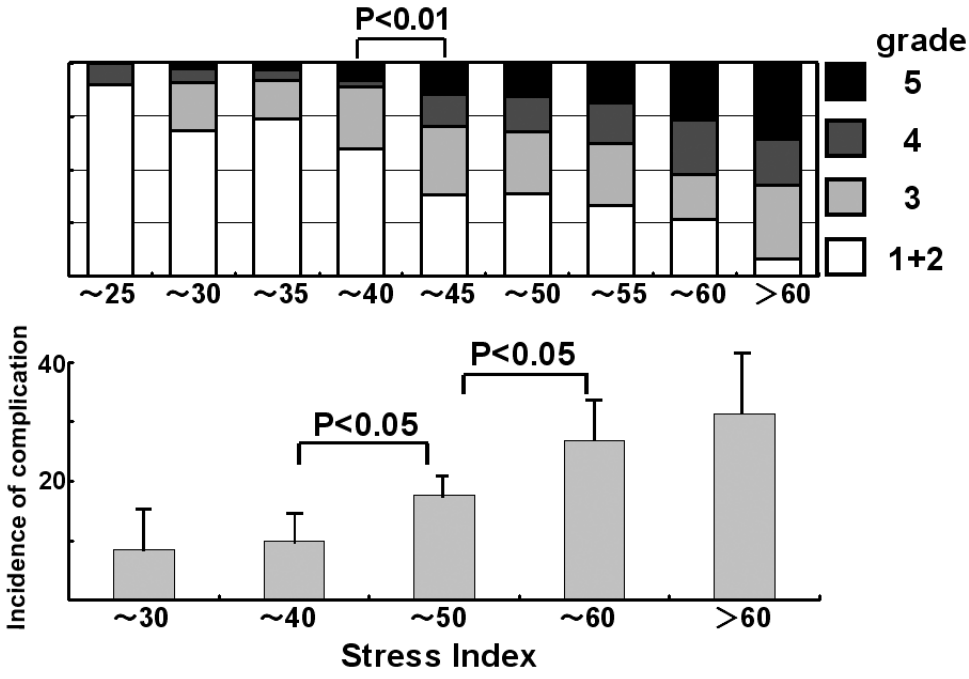

Fig. 2. *Top:* Relationship between neurological grade on admission and SI. Proportion of poor grade patients increases in higher SI group, and statistically significant difference is present between groups with SI above and below 40. *Bottom:* Relationship between incidence of systemic complications and SI. There are two significantly different points at SI 40 and 50. These SI scores may well be used as indices of high risk for systemic complications despite patient's neurological condition

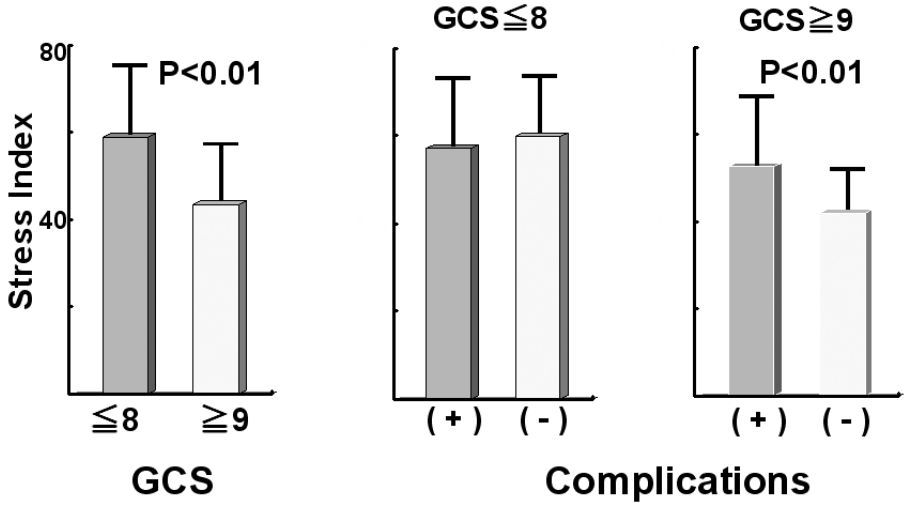

Fig. 3. *Left:* Mean SI of G-ill and G-well. There is a significant difference ($P < 0.01$) between the two groups (57.2 ± 21.3 vs 44.2 ± 16.4). *Mid:* Mean SI of G-ill with or without complications. No significant difference is present between the two groups (56.4 ± 17.1 vs 59.9 ± 19.1, respectively). *Right:* Mean SI of G-well with or without complications. The former is significantly higher ($P < 0.01$) than the latter (52.7 ± 18.2 vs 44.2 ± 16.4, respectively)

Discussion

Although management of patients suffering SAH at acute stage has been improved steadily in recent years, mortality still exceeds more than one third of overall patients and only less than a quarter of patients with SAH can make a complete recovery [4]. The major cause of mortality and morbidity from SAH can be

attributed to direct brain damages by SAH per se, rebleeding from the ruptured aneurysm or vasospasm. However, in recent studies it has been recognized that nearly a quarter of overall deaths from SAH was due to systemic complications [9]. These life-threatening complications are caused by sympathetic hyperactivity which occurs immediately after the onset of SAH and brings about excess discharge of CA [1–8]. The pathophysiological mechanism of this drastic activation of the sympathetic system concurring with SAH is assumed to be due to damages to the tissue around the anterior hypothalamus [1, 6, 8]. Neil-Dwyer and Doshi [6] reported that histological changes of the hypothalamus in patients who had died following SAH consisted of small perivascular hemorrhages, distensions of perforated vessels with small ball hemorrhages, oedema or the vessel walls involving the endothelial cells with perivascular cuffing of polymorpholeucocytes and microinfarction. Even complete infarction of the hypothalamus was observed in some cases. These hypothalamic lesions are supposed to be induced by ischemic insults due to spasm of the small vessels which supply the region [5, 6]. Although in the literature there are numbers of reports describing that an elevation of CA is sustained throughout the acute phase for more than a week after SAH [2–6], data which are shown here clearly demonstrate that plasma CA rose up once to an extremely high level immediately after the bleeding, and then returned to normal range fairly quickly within 12 to 24 hours (Fig. 1). Discrepancies between the results of the literature and the presented data can be explained by our study method using blood samples obtained only at the time of patients' arrival, in order to avoid the influence of stresses on patients caused by surgical, medical and/or examination procedures, while those used in the literature were obtained on and after admission when patients may have been exposed to stressful procedures. Consequently, as we did not examine the change of plasma CA level after admission, our data can only delineate the features of CA surge at initial or super-acute stage after SAH. Moreover, it seems quite feasible that many patients with SAH might suffer from prolonged sympathetic hyperactivity, or more generally speaking, dysfunction of the autonomic nervous system for a certain period of time, because they have actual tissue damages in the hypothalamus as shown histopathologically in the literature [1, 6]. Some authors mentioned the acceleration of vagal as well as of sympathetic activity at 4–5 days after onset of SAH, which might well be explained by these parenchymal lesions [2]. So, although our data undoubtedly demonstrates that abnormally elevated plasma norepinephrine and epinephrine levels, which are induced by the initial impact of SAH per se to the hypothalamus, are lowered quickly toward the normal range within 24 hours after bleeding, there might be a secondary effect of autonomic derangement which possibly is prolonged and may well influence, at least to some extent, the evolution of vasospasm [5].

In ordinary clinical setting, it is not easy to evaluate accurately the extent of sympathetic activity. However, judging from similarity of the time course of SI to that of plasma CA (Fig. 1) and a good statistical correlation between these two parameters as mentioned above, it is not arbitrary to say that one can grossly estimate sympathetic activity by calculating SI from BS and K^+, both of which can be easily and quickly measured in the emergency room [7, 8]. By using SI as an indicator of plasma CA level, we can demonstrate a relationship between neurological state and sympathetic activity at acute stage. The group of patients with SI over 40 comprises significantly larger numbers of neurologically ill patients than the group with SI less than 40 does (Fig. 2, top). Namely, SI over 40 means that the patients are quite ill due to systemic sympathetic hyperactivity and at the same time because of their neurological condition.

In this study, we adopted 5 typical cardiopulmonary dysfunctions as systemic complications caused by SAH, that involve NPE, apnea, cardiac insufficiency, VT/VF or ischemic ST/T change on ECG. Among those, NPE and cardiac insufficiency may occur simultaneously or in isolation [4]. Both NPE and electrocardiographic abnormalities are transient and observed only in the acute phase [4], that is corresponding well to the rise and fall pattern of plasma CA level demonstrated here (Fig. 1). A study as to relationship between SI and incidence of complications demonstrated that significant difference is observed between the groups with SI below and above 40, and also between those below and above 50 (Fig. 2, bottom). The presence of these 2 inflexion points of SI is compatible with a difference in G-well with or without complication, of which mean SI is 52.5 and 41.9, respectively (Fig. 3, right columns). Mean SI is significantly higher in G-ill than G-well (Fig. 3, left columns). Restricting to G-ill, however, average SI is not different between the cases with or without complications (Fig. 3, columns in the mid). On the other hand in G-well, mean SI is signifi-

cantly higher in those with complications than without (Fig. 3, right columns). From these data, we can conclude that physicians treating patients with SAH at acute stage should pay much attention to possible cardiopulmonary complications in those who show high SI above 50 though their neurological condition can be assessed in G-well as well as in G-ill. Actually, a precise analysis restricted to the patients who belong to grade 1 or 2 revealed that mortality of 157 patients with SI over 40 was 10.8% and that of 64 patients with SI over 50 was 14.1%, and those figures were significantly worse ($P < 0.05$ and $P < 0.01$, respectively) than mortality of 5.0% in 278 patients of grade 1 or 2 with SI lower than 40.

Conclusion

Sympathetic hyperactivity at acute stage of SAH can be grossly estimated with SI, which is easily computed from serum BS and K^+. SI over 40 may well be used as an index showing the borderline between patients suffering considerable neurological insults as well as systemic ones and those not. Regarding patients in G-well, SI over 50 suggests that there may be a formidable risk for systemic complications even in cases with good neurological condition.

References

1. Dilraj A, Botha JH, Rambiritch V, Miller R, van Dellen JR (1992) Levels of catecholamine in plasma and cerebrospinal fluid in aneurysmal subarachnoid hemorrhage. Neurosurgery 31: 42–51
2. Kawahara E, Ikeda S, Miyahara Y, Kohno S (2003) Role of autonomic nervous dysfunction in electrocardiographic abnormalities and cardiac injury in patients with acute subarachnoid hemorrhage. Circ J 67: 753–756
3. Lambert G, Naredi S, Edén E, Rydenhag B, Friberg P (2002) Sympathetic nervous activation following subarachnoid hemorrhage: influence of intravenous clonidine. Acta Anesthesiol Scand 46: 160–165
4. Macmillan CS, Grant IS, Andrews PJD (2002) Pulmonary and cardiac sequelae of subarachnoid hemorrhage: time for active management? Intensive Care Med 28: 1012–1023
5. Naredi S, Lambert G, Edén E, Zäll S, Runnerstam M, Rydenhag B, Friberg P (2000) Increased sympathetic nervous activity in patients with nontraumatic subarachnoid hemorrhage. Stroke 31: 901–906
6. Neil-Dwyer G, Cruickshank JM, Doshi R (1990) The stress response in subarachnoid hemorrhage and head injury. Acta Neurochir, [Suppl] 47: 102–110
7. Satoh A (1998) Clinicopathological features and treatment of severely ill patients with subarachnoid hemorrhage. Jpn J Neurosurg 7: 24–31
8. Satoh A, Nakamura H, Kobayashi S, Miyata A, Wada M, Tsuru K (2004) Significance of assessment of both intracranial and systemic insults in treatment of severely ill patients with acute subarachnoid hemorrhage. Surg Cereb Stroke 32: 97–102
9. Solenski NJ, Haley ECJ, Kassell NF, Kongable G, Germanson T, Truskowski L, Torner JC (1995) Medical complications of aneurysmal subarachnoid hemorrhage: a report of the multicenter, cooperative aneurysmal study. Participants of the Multicenter Cooperative Aneurysmal Study. Crit Care Med 23: 1007–1017

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