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Cytokine Levels in Cerebrospinal Fluid and Delayed Ischemic Deficits in Patients with Aneurysmal Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) induces an inflammatory reaction and may lead to ischemic brain damage. The pathogenesis of brain dysfunction and delayed ischemic symptoms remain difficult to understand despite extensive surveys of such reactions. Cytokine production in the central nervous system following SAH and its relation with clinical outcome have hardly been studied. This study was aimed to determine whether the levels of IL-1β, IL-6 and TNF-α in the initial cerebrospinal fluid would increase following aneurysmal SAH, and be related with development of delayed ischemic deficit and clinical outcome. Nineteen patients suffering from aneurysmal SAH and 12 control volunteers were the subjects in this study. Cerebrospinal fluid samples were obtained on admission and the levels of each cytokine were determined with enzyme-linked immunosorbent assay. Patients with aneurysmal subarachnoid hemorrhage showed elevated levels of IL-1β, and TNF-α on admission. The patients with poor neurological status showed high levels of IL-1β, and IL-6. The patients who developed delayed ischemic deficit had high level of IL-6. We suggest that elevated level of IL-6 in cerebrospinal fluid of patients with aneurysmal SAH on admission can predict the high risk of delayed ischemic deficit.

Key Words : *Cytokines; Interleukin-1, Interleukin-6, Tumor Necrosis Factor; Subarachnoid Hemorrhage, Delayed Ischemic Deficit*

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INTRODUCTION

Cerebral vasospasm following subarachnoid hemorrhage (SAH) due to a ruptured aneurysm is an important cause of cerebral ischemia, and is the leading cause of death and disability after aneurysmal rupture (1-3). The pathogenesis of this condition is poorly understood, and many studies have failed to yield conclusive evidence as to the causative agent or the nature of the cerebral arterial narrowing (1, 2, 4-9).

Immune responses including cytokines are involved in the pathogenesis of cerebral vasospasm following aneurysmal SAH (10, 11). Localized brain immune responses lead to increased levels of the immunomodulators, "cytokines". In experimental ischemia, the proinflammatory cytokine interleukin-1 (IL-1) mediates cellular damage and an IL-1 antagonist reduce brain damage after episode of temporary ischemia (11). Interleukin-6 (IL-6) is significantly increased in patients suffering from a delayed ischemic deficit following SAH (11). Interleukin-1 receptor antagonist (IL-1Ra) and tumor necrosis factor-α (TNF-α) are also increased following SAH. IL-1 and TNF-α are known to cause or contribute to experimental ischemic and traumatic brain injury (12).

Cho et al. (13) reported that increased levels of IL-1β, IL-6, IL-8, and TNF-α could be highly suggestive of meningitis. IL-1β production in the central nervous system (CNS) following SAH has not been studied. In addition, the initial levels of cerebrospinal fluid (CSF) cytokines including IL-1β, IL-6, and TNF-α contributing to delayed ischemic deficit (DID) have not been studied. On the basis of the known association of SAH and various cytokines, this study was undertaken to investigate whether DID could be predicted by the high levels of cytokines including IL-1β, IL-6, and TNF-α in the initial CSF following SAH (10, 11).

MATERIALS AND METHODS

Nineteen patients (Table 1) suffering from aneurysmal SAH were the subjects in this study. CSF samples were obtained at emergency room, less than 24 hr after attack. CSF was obtained in 12 patients undergoing induction of spinal anesthesia for surgery of inguinal hernia. These 12 patients served as control volunteers (Table 2). Each CSF sample was immediately centrifuged and stored at -80°C until analysis. The level of each cytokine was analyzed with enzyme-linked immunosorbent assay (ELISA) (supplied by Diaclone Research, Besancon, France). Incubations of CSF and stan-

Table 1. Clinical characteristics of 19 patients with subarachnoid hemorrhage

Case No.	Age (yr)/ Sex	Aneurysm*	HHG†	FG‡	DID	GOS§
1	56/F	Acom	4	3	no	3
2	69/F	MCA	3	4	no	5
3	36/M	Pcom	2	1	yes	4
4	34/F	MCA	1	2	no	5
5	47/M	Acom	3	3	yes	4
6	56/F	ICA	2	3	no	4
7	62/M	Acom	2	3	no	5
8	64/F	Pcom	3	2	yes	3
9	48/M	Acom	3	2	no	5
10	52/F	Pcom	4	2	yes	2
11	44/F	VA	3	2	no	4
12	38/F	Acom	2	3	no	5
13	47/F	MCA	3	4	no	5
14	58/M	Acom	3	3	yes	4
15	49/F	Pcom	2	3	no	5
16	73/F	Acom	4	3	no	1
17	51/M	Acom	1	1	yes	3
18	42/F	Pcom	2	1	no	5
19	56/F	DACA	3	3	no	5

*Aneurysm: Acom; anterior communicating artery, MCA; middle cerebral artery, ICA; internal carotid artery, Pcom; posterior communicating artery, VA; vertebral artery, DACA; distal anterior cerebral artery. †Hunt and Hess grade (14) 1. asymptomatic or minimal headache and slight nuchal rigidity. 2. moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy. 3. drowsiness, confusion, or mild focal deficit. 4. stupor, moderate to severe hemiparesis, possible early decerebrate rigidity and vegetative disturbances. 5. deep coma, decerebrate rigidity, moribund appearance. ‡Fisher grade (15) 1. no blood detected. 2. diffuse or vertical layers<1 mm thickness. 3. localized clot and/or vertical layer>1 mm thickness. 4. intracerebral or intraventricular clot with diffuse or no SAH. §Glasgow outcome scale (16). 1. death. 2. persistent vegetative state. 3. severe disability (conscious but disable). 4. moderate disability (disabled but independent). 5. good recovery

dards with conjugates were performed according to the instructions of the manufacturer, using only half the volumes. Substrate activation by horseradish peroxidase was determined by chemiluminescence (Microplate reader manufactured by Bio-Rad Inc., Japan). Tetramethylbenzidine (100 μL, 0.1 mg/L) was added and the solution was incubated for 20 min. The plate was then placed in a luminometer and 50 μL of 6 mM Na Luminol (supplied by Diaclone Research, Inc., Besancon, France) which had been recrystallized three times and stabilized with hydrogen peroxide, was added to each well. Emitted light was measured by means of a photomultiplier with a spectral response of 450 to 620 nm. The signal was measured at a peak over a total time period of 1 second. Light signals over background values were detected linearly related in a log scale in the 15.6 to 500 pg/mL interval of IL-1β, 6.25 to 200 pg/mL interval of IL-6 and 25 to 800 pg/mL interval of TNF-α in standard curve.

All patients were treated with early surgery, nimodipine, and intensive "triple H" therapy (hypervolemia, hypertension, and hemodilution). All operations were performed by a single neurosurgeon (BCJ) so as to exclude operator-related variation.

Table 2. CSF cytokine levels of control volunteers

No.	Age (yr)/Sex	IL-1β (pg/mL)	IL-6 (pg/mL)	TNF-α (pg/mL)
1	47/F	0.1	589.1	7.5
2	36/M	3.2	804.4	4.2
3	52/M	0.2	676.6	2.1
4	65/F	0.9	484.9	8.4
5	29/M	0.1	552.7	11.7
6	42/F	0.1	436.6	7.2
7	38/F	0.1	641.8	10.5
8	45/M	1.0	228.5	0.2
9	46/M	0.5	522.9	0.2
10	58/F	0.1	206.2	0.2
11	53/F	0.1	157.0	0.2
12	47/F	0.1	204.0	0.2
Mean±SD	46.5	0.54±0.90	458.73±214.11	4.38±4.45

The level of each cytokine in SAH patients was compared with that of control volunteers. The level of each cytokine was analyzed in relation to various parameters, such as neurological status on admission, amount of SAH on computerized tomographic (CT) scan, development of DID and clinical outcome. The patients' neurological status on admission were classified according to Hunt and Hess grading (HHG). HHG score of 1 to 3 was regarded as low-grade group, suggesting relatively good neurological condition. HHG score of 4 or 5 was regarded as high-grade group, suggesting poor neurological condition. Amount of SAH on CT scan was classified according to Fisher's grade (FG). FG score of 1 to 2 was regarded as low-grade group, indicating small amount of hemorrhage on a CT scan and FG score of 3 to 4 was regarded as high-grade group, indicating large amount of hemorrhage on a CT scan. All patients took CT scan at 14th day after SAH to find out radiological evidence of DID. The patients who developed DID were compared with those without DID. Clinical outcome was classified according to Glasgow outcome scale (GOS). GOS score of 4 to 5 was regarded as favorable outcome and GOS score of 1 to 3 was regarded as unfavorable outcome.

The ages of the patients ranged from 34 to 69 yr (mean, 51.7 yr). Five patients were over sixty years. Six patients were men and 13 patients were women. The aneurysmal rupture in nine cases developed at anterior communicating artery. Sixteen patients presented with low HHG, others with high HHG. Eleven patients showed high FG. Six patients developed DID. Fourteen patients had favorable outcome and others had unfavorable outcome (Table 1).

Statistical analyses were done using Mann-Whitney U-test (p<0.05). Analyses were performed using IBM compatible computers (Sambo computer Inc., Seoul, Korea) and SPSS software (SPSS Inc., U.S.A.).

RESULTS

Cytokine levels of control volunteers

In control volunteers, the ages ranged from 29 to 65 yr (mean, 46.5 yr). Seven were women, and five were men. The variation of each cytokine was smaller than that in SAH patients. Mean values±SD for IL-1β, IL-6, and TNF-α were 0.54±0.90 pg/mL, 458.73±214.11 pg/mL, 4.38±4.45 pg/mL, respectively (Table 2).

Cytokine levels of SAH patients

CSF samples from the 19 patients were analyzed for IL-1β, IL-6, and TNF-α. A large variation in individual cytokine value was found in SAH patients. Mean values±SD for IL-1β, IL-6 and TNF-α were 86.82±179.39 pg/mL, 630.15 ±685.41 pg/mL, 42.98±30.08 pg/mL, respectively. The mean values of IL-1β, IL-6 and TNF-α increased compared with controls. Three patients (cases 3, 6, and 8) had high levels of IL-1β and two of them developed DID. Seven patients (cases 3, 5, 6, 8, 10, 14 and 17) had high levels of IL-6 and 6 of them (cases 3, 5, 8, 14, and 17) developed DID. Three of 6 patients who developed DID had poor outcome. Three (cases 5, 6, and 14) of 7 patients who had high levels of IL-6 showed a large amount of SAH (Table 3).

Comparison between SAH patients and control volunteers

Acording to the present study, the mean values of IL-1β and TNF-α in SAH patients were around 10-fold higher than those in healthy volunteers. A statistically significant increase of the level was detected in IL-1β and in TNF-α (p<0.05, Mann-Whitney U test) in patients with SAH. The mean value of IL-6 in SAH patients was higher than that in healthy volunteers, but without a statistical significance (p> 0.05; Table 4).

Table 3. Cerebrospinal fluid cytokine levels of 19 patients with subarachnoid hemorrhage

Case No.	IL-1β (pg/mL)	IL-6 (pg/mL)	TNF-α (pg/mL)
1	12.5	148.64	33.33
2	25.0	40.54	16.67
3	750.0	1851.35	133.33
4	12.5	54.05	16.67
5	37.5	1310.81	16.67
6	337.5	1567.56	16.67
7	37.5	94.59	33.33
8	187.5	1216.21	33.33
9	25.0	67.56	33.33
10	12.5	1540.54	66.67
11	50.0	27.02	33.33
12	25.0	364.86	50.00
13	12.5	162.16	50.00
14	25.0	1297.29	100.00
15	12.5	13.51	50.00
16	12.5	189.18	33.33
17	12.5	1554.05	50.00
18	25.0	13.51	16.67
19	37.0	456.45	33.33
Mean±SD	86.82±179.39	630.15±685.41	42.98±30.08

Hunt and Hess grade

The mean value IL-1β in low HHG group (n=16) was 2.5±0.00 pg/mL. In high HHG group (n=3), the mean value of IL-1β was 100.75±193.15 pg/mL which was around 40-fold higher than that of low HHG group with a statistical significance (p<0.05). For IL-6, the mean value in low HHG group was 117.11±91.98 pg/mL. In high HHG group, the mean value of IL-6 was 726.35±707.18 pg/mL, which was around 6-fold higher than that of low HHG group, but without a statistical significance (p>0.05). There was no statistically significant difference between the levels of TNF-α in low HHG group and in high HHG group (42.71±32.18 pg/mL and 44.44±19.25 pg/mL, respectively; p>0.05; Table 5).

Fisher grade

The mean value of IL-1β in low FG group (n=8) was 134.36±255.63 pg/mL. In high FG group (n=11), the mean value of IL-1β was 52.23±95.16 pg/mL, which was around one third of that of low FG group, but without a statistical significance (p>0.05). The mean value of IL-6 in low FG group was 599.66±797.64 pg/mL. In high FG group, the mean value of IL-6 was 652.33±631.65 pg/mL, which was higher than that of low FG group, but without a statistical significance (p>0.05). The mean value of TNF-α in low FG group was 47.92±38.25 pg/mL. In high FG

Table 4. Comparison of each CSF cytokine level between patients with subarachnoid hemorrhage and control volunteers

Cytokine	SAH* (n=19)	Control (n=12)	$p^{\dagger}$
IL-1β	86.82±179.39	0.54±0.90	0.000
IL-6	630.15±685.41	458.73±214.11	0.441
TNF-α	42.98±30.08	4.38±4.45	0.000

*Subarachnoid hemorrhage; †Mann-Whitney U test (p<0.05)

Table 5. Comparison of Hunt and Hess grade with CSF cytokine levels

Cytokine	Low HHG (n=16)	High HHG (n=3)	p^{*}
IL-1β	2.5±0.00	100.75±193.15	0.037
IL-6	117.11±91.98	726.35±707.18	0.655
TNF-α	42.71±32.18	44.44±19.25	0.561

*Mann-Whitney U test (p<0.05)

group, the mean value of TNF-α was 39.39±23.89 pg/mL, which was lower than that of low FG group, but without a statistical significance (p>0.05; Table 6).

Delayed ischemic deficit

The mean value of IL-1β in DID group (n=6) was 170.83 ±291.51 pg/mL. In non-DID group (n=13), the mean value of IL-1β was 48.04±87.78 pg/mL. The mean value of IL-1β in DID group was around 3-fold higher than that of non-DID group, but without a statistical significance (p>0.05). The mean value of IL-6 in DID group was 1207.20 ±629.14 pg/mL. In non-DID group, the mean value of IL-6 was 363.82±544.45 pg/mL. The mean value of IL-6 in DID group was around 4-fold higher than that of non-DID group, and the difference was statistically significant (p<0.05). The mean value of TNF-α in DID group was 66.67±43.46 pg/mL. In non-DID group, the mean value of TNF-α was 32.05±12.66 pg/mL, which was a half of that of DID group, without statistical significance (p>0.05; Table 7).

Glasgow outcome scale

The mean value of IL-1β in unfavorable GOS group (n=5) was 47.5±78.26 pg/mL. In favorable GOS group (n=14), the mean value of IL-1β was 100.86±204.61 pg/mL, which was higher than that of unfavorable GOS group, but without a statistical significance (p>0.05). The mean value of IL-6 in unfavorable GOS group was 623.32±707.71 pg/mL. In favorable GOS group, the mean value of IL-6 was 632.24 ±704.52 pg/mL, which was slightly higher than that of the unfavorable (p>0.05). The mean value of TNF-α in unfavorable GOS group was 43.33±14.91 pg/mL. In favorable GOS group, the mean value of TNF-α was 42.86±34.41 pg/mL, which was slightly lower than that of unfavorable GOS group (p>0.05; Table 8).

Table 6. Comparison of Fisher grade with CSF cytokine levels

Cytokine	Low FG* (n=8)	High FG* (n=11)	$p^{\dagger}$
IL-1β	134.36±255.63	52.23±95.16	0.732
IL-6	599.66±797.64	652.33±631.65	0.967
TNF-α	47.92±38.25	39.39±23.89	0.764

*Low FG: Fisher grade 1 and 2, high FG: Fisher grade 3 and 4; †Mann-Whitney U test (p<0.05)

Table 7. Comparison of delayed ischemic deficit with CSF cytokine levels

Cytokine	DID* (n=6)	no DID† (n=13)	$p^{\ddagger}$
IL-1β	170.83±291.51	48.04±87.78	0.440
IL-6	1207.20±629.14	363.82±544.45	0.003
TNF-α	66.67±43.46	32.05±12.66	0.062

*DID: development of delayed ischemic deficit; †no DID: no development of delayed ischemic deficit; ‡Mann-Whitney U test (p<0.05)

Table 8. Comparison of Glasgow outcome scale with CSF cytokine levels

Cytokine	GOS* (1-3, n=5)	GOS (4-5, n=14)	$p^{\dagger}$
IL-1β	47.5±78.26	100.86±204.61	0.103
IL-6	623.32±707.71	632.24±704.52	0.195
TNF-α	43.33±14.91	42.86±34.41	0.413

*GOS (1-3) was regarded as unfavorable outcome, GOS (4, 5) as favorable outcome; †Mann-Whitney U test (p<0.05)

DISCUSSION

SAH induces cascading biochemical reactions and may cause major brain damage (11). The pathogenesis of brain dysfunction and delayed ischemic symptoms remain elusive despite continuing investigations. A change in metabolism, increased levels of excitatory amino acids, ischemic changes, and inflammatory phenomena have been described. In addition, cerebral vasospasm, which often coexists with symptoms of delayed ischemia, has been thought to play a causative role by some researchers. Cerebral vasospasm after SAH results from vascular smooth muscle contraction and morphologic changes related to inflammatory reactions (12, 17). Inflammatory mechanisms appear to be important in causing symptoms of clinical deterioration and ischemic brain damage following a SAH (11).

Most cytokines usually act over short distances as autocrine or paracrine intercellular signals in local tissues. Experimental injuries caused an early production of cytokines (18). Another experimental brain contusion caused a delayed intracerebral production of potent inflammatory cytokines such as IL-1β, IL-6, and TNF-α. An increase of the proinflammatory cytokines, IL-1β, IL-6, or TNF-α was also detected in the CSF of patients treated for severe brain injuries (10, 11, 19-22).

The inflammatory cytokines are differently released in the intrathecal space infected with viruses or bacteria and persistent increase of cytokines is associated with continued disease activity (20). Each of concentrations of IL-1β, IL-6, IL-8, and TNF-α was significantly increased in the CSF of patients with viral or *Mycoplsma pneumoniae* meningitis (13). Both concentrations of IL-1β and TNF-α were significantly higher in the CSF of patients with bacterial meningitis than in those with aseptic meningitis (19-21). Increased serum TNF-α concentration was associated with fatal outcome in meningococcal septic shock (20, 21). A significant correlation was found between TNF-α concentration in the CSF, and the consecutive febrile days or the occurrence of seizures in bacterial meningitis (22). IL-1β and TNF-α are produced in the purulent CSF, and their concentrations may be associated with the initial clinical status and the outcome (20).

SAH causes an inflammatory reaction and may lead to ischemic brain damage (11). Experimental ischemia has been shown to be connected with the alarm-reaction cytokines such as IL-1 Ra and TNF-α (11). Increased levels of these cytokines were detected in patients following SAH event and correlated with neurological damage. It is likely that these cytokines, especially IL-1, contribute to experimental ischemic and traumatic brain injury. IL-6 level were significantly increased in patients suffering from a DID, which may have immunological causes or reflect alterations of the immune system (10). However, interleukin-1β production in the CNS following SAH has not been studied. In addition, initial levels of CSF cytokines including IL-1β, IL-6, and TNF-α as strong candidates contributing to DID have not been studied. On the basis of the known association of SAH and various cytokines, this study was undertaken to investigate whether DID could be predicted by the high levels of cytokines including IL-1β, IL-6, and TNF-α in the initial CSF following SAH.

The results of this study demonstrated that the majority of patients with ruptured cerebral aneurysms have increased cytokine levels in the initial CSF on admission. The levels of IL-1β, IL-6, and TNF-α in CSF were higher in patients with SAH (n=19) than in healthy volunteers (n=12). In particular, IL-1β and TNF-α levels were significantly increased in CSF from SAH patients on admission (p=0.000, 0.000, respectively). However, IL-6 levels showed no statistically significant difference (p=0.441). A large variation in individual IL-6 was revealed. These results could be explained by the previous report that showed CSF IL-1β and TNF-α levels were increased at early stage of inflammatory cascade and they induced IL-6 expression in SAH patients (11).

The importance of assessing the neurological condition in patients with SAH lies in the prediction of outcome (23). Cytokine production in the CNS following SAH and its relation with initial neurological condition have not been studied. The present study revealed that IL-1β and IL-6 levels were markedly elevated in high HHG group (n=3) than in low HHG group (n=16), but only IL-1β had a statistical significance (p=0.037). Most patients with good neurological condition had low levels of IL-1β and IL-6, while all the patients with poor neurological condition had high levels of them. HHG relies on less consistent definition of level of consciousness than does the Glasgow coma scale (14). The IL-6 is increased in the ventricular fluid of patients suffering from head injury and the levels correlate with clinical status (24). It is likely that IL-1β and IL-6 may be considered to be indicators of initial poor neurological status after an SAH event.

Focal, thick collections of cisternal blood visualized on a CT scan are highly predictive of vasospasm (25). The present study showed that the levels of IL-1β and TNF-α in low FG group (n=8) were higher than in high FG group (n=11), and the level of IL-6 in high FG group were higher than in low FG group without a statistical significance. It is unlikely that the levels of IL-1β, IL-6, and TNF-α in the initial CSF after SAH correlate with amount of cisternal blood visualized on a CT scan. However, the relationship between amount of hemorrhage on a CT scan and cytokine levels should be further verified with prospective studies in aneurysmal SAH patients.

Pathogenic role of the immune system in vasospasm and DID after SAH has been postulated by some authors (1, 8), while others have failed to reveal its causative role (7). Different mechanisms of the immune system have been believed to be operative in DID. One of them is based on the observation that the neopterin values were higher in patients suffering from symptoms of delayed cerebral ischemia (5). This can be interpreted as signs of ongoing T cell activation both systemically and in the CSF compartment following SAH. This study demonstrated that six patients developed DID. The levels of IL-1β, IL-6, and TNF-α were markedly elevated in these patients (n=6) than the patients without DID (n=13), but only IL-6 levels showed a statistical significance (p=0.003). A large variation in individual levels of IL-1β and TNF-α was found. Of seven patients who had levels of IL-6 higher than 1216.21 pg/mL in the initial CSF, six patients developed delayed ischemic symptoms and showed a focal or diffuse infarction on follow-up CT scan. Two patients of them developed moderate disability and one patient experienced severe disability. Three patients attained good recovery. These results indicate that high level of IL-6 in the initial CSF on admission after SAH event can predict DID. Mathiesen et al. (10) reported that IL-6 levels were significantly increased in patients suffering from DID following SAH. The intracerebral levels of IL-6 appeared to be two peak pattern. First peak is day 3, and second is around day 6 following ictus. The DID, most commonly noticed 4 to 8 days after SAH, follows a similar time course and is frequently heralded by an increased leukocyte count in peripheral blood and a low-grade fever. The IL-6 levels were higher on day 6 than on day 3 and day 9. More recently, they showed that levels of IL-1 receptor antagonist and TNF-α were increased after SAH event and high cytokine levels correlated with brain damage (11). It is likely that these cytokines, especially IL-1, contribute to brain damage after SAH event. Our results showing elevated levels of IL-1β, IL-6, and TNF-α are consistent with their findings, but only IL-6 exhibited a statistical significance.

Mathiesen et al. (10) also detected significant activation of the alarm-reaction cytokine system demonstrated by measurements of IL-1Ra and TNF-α levels in CSF obtained from patients suffering from SAH. The results showed that patients with favorable outcomes had low levels of these cytokines. This study also showed that the patients with good GOS (n=14) showed high levels of IL-1β and IL-6 in the initial CSF, while the patients with poor GOS (n=5) showed high levels of TNF-α in the initial CSF, but with-

out a statistical significance. Three of 5 patients (cases 1, 8, 10, 16, and 17) who had poor GOS showed high levels of IL-6 in the initial CSF after SAH event. Two of them (cases 1, 16) did not show elevation of IL-6 levels and did not develop DID. Two patients, whose IL-6 level was not increased, but developed DID, showed poor outcomes. One (case 1) of them had a de novo aneurysmal rupture, followed by moderate disability. Another (case 16) experienced disseminated intravascular coagulation, which lead to death. It is unlikely that the levels of these cytokines in initial CSF on admission after SAH event can predict the outcome. We assume that the outcome would be determined by multiple factor, e.g, operative complications, rebleeding, combined medical condition, hydrocephalus, etc. Strong correlations were found between IL-1β and IL-6 levels in the initial CSF, and neurological condition on admission, and between IL-6 levels in the initial CSF on admission and development of DID.

In conclusion, the present study revealed that patients with aneurysmal SAH on admission exhibited increased levels of IL-1β and TNF-α, and the patients presenting with poor neurological condition had high levels of IL-1β and IL-6 in their initial CSF. It is likely that high levels of IL-6 in the initial CSF on admission after SAH event can predict the high risk of DID. These findings are in support of the hypothesis that deterioration following SAH may have immunological causes or reflect alterations of the immune system. However, further corroboration of such hypothesis is needed, and further neuroimmunological research is necessary to analyze the time course of IL-1β, IL-6, and TNF-α in CNS after SAH event.

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