CLINICAL ARTICLE

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Correlation between Cerebral Vasospasm after Subarachnoid Hemorrhage and Intercellular Adhesion Molecule-1 Levels in Serum and Cerebrospinal Fluid

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Objective : The purpose of this study is to evaluate the correlation of the ICAM-1 levels in serum and CSF with cerebral vasospasm in early aneurysmal subarachnoid hemorrhage (SAH) patients.

Methods : A prospective analysis was performed in thirty consecutive patients who underwent early surgery for intracranial aneurysmal SAH. The serum and CSF were obtained daily through the indwelling arterial lines and intraoperative ventriculostomy, or cisternal drain for 4 consecutive days after surgery. The ICAM-1 levels in serum and CSF samples were measured via quantitative enzyme-linked immunosorbent assay.

Results : The mean concentration of serum in aneurysmal SAH patients was 207.89ng/ml compared with 132.25ng/ml in controls. The mean concentration of CSF in aneurysmal SAH patients was 76.39ng/ml compared with 3.96ng/ml in controls. There were no significant differences between serum and CSF ICAM-1 level with regards to clinical characteristics in patients with aneurysmal SAH ($P>0.05$). However, CSF ICAM-1 levels increased significantly in patients with vasospasm compared with those without vasospasm ($P<0.05$).

Conclusion : The major result of this study shows that ICAM-1 is increased in CSF after early aneurysmal SAH and that this increase in ICAM-1 has correlation with cerebral vasospasm. Further study is needed to determine whether ICAM-1 levels may be indicator in the pathogenesis of important events leading to cerebral vasospasm.

KEY WORDS : Intercellular adhesion molecule-1 · Vasospasm · Aneurysmal subarachnoid hemorrhage.

Introduction

Despite considerable advances in the diagnosis and treatment of subarachnoid hemorrhage(SAH), the overall outcome has been poor[8]. Cerebral vasospasm has been a significant factor of adverse outcome and the leading potentially curable cause of death and disability in patients with aneurysmal SAH[24]. Earlier detection of symptomatic vasospasm might allow optimally prophylactic treatment to prevent cerebral ischemia[24]. However, the pathogenesis of the cerebral vasospasm after aneurysmal SAH are is not yet known[30].

Recently, some investigators thought that the cerebral vasospasm is caused by certain complicated inflammatory processes of the subarachnoid space[9,10]. For instance, cerebrovascular complications have been frequently accompanied by bacterial meningitis. In addition, nonspecific inflammation of the subarachnoid space produced by substances, such as talc or beads (latex or dextran), result in marked arterial constriction and vascular morphological changes mimicking those seen after SAH[8,21].

Adhesion molecules consist of an evolving set of macromolecules which mediate the white cell response to injury through adherence to the vascular endothelium[46] and encompass a collection of related molecules that share the ability to influence immune and inflammatory responses. Appearance or upregulation of several glycoproteins implicated as adhesion molecules has been seen in ischemiareperfusion injury in the brain[2,4,14], but little work has been done to investigate the role of adhesion molecules in delayed ischemia after SAH.

Intercellular adhesion molecule-1 (ICAM-1) is a proinflammatory marker[2,38]and a member of the immunoglobulin superfamily which is located in the vascular endothelium

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and binds to the CD18 complex on circulating leukocytes[14,33]. ICAM-1 expression can be stimulated by various cytokines including lipopoly-sacharides, tumor necrotic factor-α, interferon gamma, and interleukin-1[25,32,33]. ICAM-1 is thought to mediate adherence and transendothelial migration of neutrophils in areas of inflammatory tissue[7,23].

Recently, a role for ICAM-1 in the pathogenesis of cerebral vasospasm after SAH has attracted limited experimental attention[14,42,49]. Sills, et al.[50], demonstrated an association between ICAM-1 upregulation and femoral artery vasospasm following vascular exposure to blood in a rat femoral artery model. In a rabbit model of SAH, Bavbek, et al.[2], demonstrated that antibodies to ICAM-1 and its ligand, CD18, attenuate basilar vasospasm. The relevance of these experimental findings to human vasospasm, however, is not yet known. Polin, et al.[45], demonstrated elevation of soluble E-selectin, ICAM-1, and vascular cell adhesion molecule-1 levels in the CSF of patients after aneurysmal SAH. Mack, et al.[31], found a correlation between serum soluble ICAM-1 levels and outcome in patients with aneurysmal SAH. These animal and human findings suggest that ICAM-1 may be involved in the pathogenesis of vasospasm.

To investigate the relationship between the development of vasospasm and ICAM-1, to determine the correlations ICAM-1 with various parameters, the author measured ICAM-1 levels in serum and cerebrospinal fluid(CSF) at serial times after ruptured aneurysmal SAH and analyzed them with respect to clinical characteristics of patients prospectively.

Materials and Methods

Patients and control groups

All 59patients underwent surgery for aneurysm obliteration from January 2003 to December 2003 at the neurosurgical department in Hanyang University Guri Hospital for ruptured intracranial aneurysms.

Surgery for aneurysm was performed within 24hours after SAH. Twenty-eight patients underwent cilpping, and the others underwent wrapping and clippng. In this study, twenty-one of these patients were excluded because of insufficient sampling and eight patients were also excluded due to incomplete data records. Thirty consecutive patients (18women and 12men), with a mean age of 54years were eligible in the study. Patients considered to have meningitis or sepsis at the time of CSF collection were excluded. However, patients with intraventricular hemorrhage were also included in this series.

Four patients without clinical or radiological evidence of SAH (two with unruptured aneurysms and two with herniated intervertebral discs) served as a control group and underwent a serum and CSF sampling at the time of admission.

Specimen preparation and analysis

Serial blood and CSF samples were collected at the same time fresh from indwelling arterial lines, or intraoperative ventriculostomy, and cisternal drain for the initial 4days after aneurysmal SAH surgery. Control CSF samples were obtained via lumbar puncture for the presence of herniated intervertebral disc, and via intraoperative ventriculostomy for unruptured aneurysms. Samples were centrifuged at 1500rpm for 10minutes as soon as possible and the resulted supernatant was collected and stored at -80°C until it was assayed. ICAM-1 levels in serum and CSF were quantitatively measured in nanograms per milliliter by using a commercially available enzyme-linked immunosorbent assay (ELISA ; R & D Systems, Minneapolis, MN). The ELISA kits provided wells coated with a monoclonal antibody to specific human adhesion molecules. An antibody to a second separate epitope was bound to an enzymatic moiety capable of catalyzing a colorimetric reaction. The observed molecular weight of the soluble form was approximately equivalent to that of the extracellular domain of the molecule and has been demonstrated to be an acceptable surrogate for endothelial ICAM-1 expression[45]. Control CSF and serum were prepared identically to those of ruptured aneurysmal SAH patients.

Clinical chlaracteristics

The patients were analyzed on the basis of clinical profiles, radiological characteristics, and intraoperative findings. Because the risk of disability, mortality, and the cost of medical care are particularly high for patients with aneurysmal SAH who are 65years of age or older, the age of patients was categorized as $<$65years and $\geq$65years[52]. The Hunt and Hess grade[20] was used as clinical grading on admission. Patients of Hunt and Hess grade III or greater was considered poor grade, the others were of good grade[40]. The amount of SAH on admission computerized tomographic(CT) scans was classified according to Fisher grade 1, 2 (i.e., none, diffuse or localized thin) or 3, 4 (i.e., diffuse or localized thick, intraventricular hemorrhage, or intracerebral hemorrhage)[12,48]. The clinical outcome was categorized according to the Glasgow Outcome Scale(GOS) as favorable (good recovery and moderate disability) or unfavorable (severe disability, vegetative state, or dead) at three month after aneurysmal operation[22]. The aneurysmal size was categorized as $<$10mm, 10 to 25mm, or $\geq$25mm. Aneurysms measuring more than 25mm in diameter were excluded from this study, because these giant aneurysms were unruptured or had insufficient sampling. The radiological presence of hydrocephalus was assessed by a neuroradiologist or neurosurgeon according to bicaudate index on admission CT scans[19].

Definition of vasospasm and vasospasm-related infarction

Cerebral angiography and transcranial Doppler(TCD) studies were performed in patients with aneurysmal SAH whenever clinically indicated throughout their hospital course. Generally, The peak incidence of angiographic vasospasm was at 1week after subarachnoid hemorrhage; on the other hand, about 60percent of patients demonstrated angiographic evidence of vasospasm during the second week.

However, clinical symptomatic manifestations are only witnessed in 20percent of aneurysmal SAH patients. The diagnosis of symptomatic vasospasm has used the criteria defined by Haley, et al.[15,16,24], as following; 1) onset of new neurological deficits such as confusion, disorientation, drowsiness, or focal motor deficit during posthemorrhage days 4 to 14; 2) negative findings on CT scans obtained to rule out other causes of neurological deterioration such as hemorrhage, cerebral edema, or hydrocephalus; 3) no other identifiable cause of neurological deterioration such as hyponatremia ($\leq$132mEq/L), hypoxia, drug toxicity, infection, or seizures; and 4) evidence of vasospasm on cerebral angiogram demonstrating vascular narrowing affecting a territory concordant with the suspected source of the change in findings on neurological examination. Cerebral infarction caused by vasospasm was diagnosed if either a delayed ischemic deficit became sustained beyond the risk period of cerebral vasospasm or if imaging studies revealed a region of cerebral infarction in vascular distribution consistent with the patient's vasospasm.

Statistical analysis

Statistical analysis was performed using a commercially available computer software program (SPSS for Windows version 10.0 : SPSS INC., Chicago, IL). The statistical procedure used for evaluating the difference of the medians between two groups of the parameters was the nonparametric Mann-Whitney U test. A Wilcoxon signed rank test was used to determine whether there were associations between vasospasm and change of ICAM-1 level. All data value were expressed as mean$\pm$standard error. A probability value of less than 0.05 was considered statistically significant.

Results

The study population consisted of 12male and 18female patients. The mean age was 54years (range 31~79) (Table 1). In the non-SAH control group (female:male = 2:2), the mean age was 49years (range 20~72years) (Table 2). As seen in Fig. 1, when compared with controls, early ICAM-1 levels in serum and CSF were elevated in the entire aneurysmal SAH patients. The mean concentration of serum in the SAH patients was 207.89 (131.82~283.99)ng/ml compared with 132.25 (117.56~148.00)ng/ml in controls. The mean concentration of CSF in the SAH patients was 76.39 (11.08~269.23)ng/ml compared with 3.96 (0.00~9.31)ng/ml in controls.

Correlation to clinical variables with serum ICAM-1 level

Sex and age

ICAM-1 levels were not markedly different in the aneurysmal SAH patients over the entire 4-day sampling period for sex and age (Table 3) (Fig. 2). And its difference was not statistically significant ($P>0.05$) (Table 3).

Hunt and Hess-grade

ICAM-1 levels were higher in poor grade than in good grade patients. ICAM-1 levels gradually decreased in good grade and poor grade patients during the first 3 sampling days (Table 3) (Fig. 3). However, this difference between good and poor grade patients was not statistically significant ($P>0.05$) (Table 3).

Fisher grade

ICAM-1 levels were markedly different in the aneurysmal SAH patients over the entire 4-day sampling period between Fisher grade 1, 2 groups and 3, 4 groups (Fig. 3) (Table 3). This difference between these two groups was statistically significant ($P<0.05$) (Table 3).

GOS

According to GOS score, ICAM-1 levels were not markedly different in the aneurysmal SAH patients over the entire 4-day sampling period between favorable or unfavorable groups (Table 3). ICAM-1 levels were generally highest at the first day after operation and declined rapidly (Fig. 4). However, this decrease between these two groups was not statistically significant ($P<0.05$).

Other factors

In regard to aneurysmal sac size, ICAM-1 levels in all patients were not markedly different between smaller and larger than 10mm sacs, even though ICAM-1 levels gradually were generally highest at the first day after operation and declined rapidly and increased again (Fig. 5) (Table 3). Its difference between these two groups was not statistically significant ($P>0.05$) (Table 3). The difference of ICAM-1 levels according to development of hydrocephalus and those of aneurysmal sac size presented no statistical significance ($P>0.05$) (Fig. 5) (Table 3).

Table 1. Demographic characteristics of in SAH patients with ruptured aneurysms*

Patient no.	Sex /Age(yr)	Aneurysm location	Hunt and Hess -grade	Fisher grade	Aneurysm sac size (mm)	Hydrocephalus	Vasospasm	GOS
1	F/48	Left MCA bifurcation	III	IV	12	Yes	Yes	MD
2	M/66	Right MCA bifurcation	IV	IV	15	Yes	Yes	D
3	M/38	Right MCA bifurcation	IV	IV	4	Yes	Yes	MD
4	F/31	ACoA	III	III	5	Yes	Yes	G
5	F/78	Left MCA bifurcation	II	III	7	No	No	G
6	F/67	Right MCA bifurcation	II	III	12	No	No	G
7	M/39	ACoA	II	III	7	No	No	G
8	F/43	Left PCoA	IV	III	12	Yes	Yes	D
9	F/55	Left PCoA	V	IV	6	Yes	Yes	SD
10	M/39	ACoA	II	III	6	Yes	Yes	G
11	F/63	ACoA	III	III	8	No	No	G
12	F/65	ACoA	IV	IV	6	Yes	Yes	D
13	F/79	ACoA	IV	IV	15	No	Yes	V
14	M/64	ACoA	II	I	12	Yes	No	G
15	M/45	Right MCA bifurcation	V	IV	20	Yes	Yes	D
16	F/47	Right MCA bifurcation	II	III	8	No	No	G
17	M/50	ACoA	III	III	8	Yes	No	G
18	F/55	Right ACA	I	II	8	No	No	G
19	M/68	ACoA	III	IV	7	Yes	No	MD
20	F/53	Right MCA bifurcation	II	III	20	Yes	Yes	G
21	F/65	Left ICA bifurcation	V	IV	7	No	Yes	V
22	M/37	Left PICA	V	IV	14	Yes	Yes	D
23	M/34	ACoA	II	II	6	No	No	G
24	M/54	ACoA	V	IV	8	Yes	Yes	D
25	F/53	Right MCA bifurcation	III	III	7	No	No	G
26	M/72	Left PCoA	III	III	8	Yes	No	G
27	F/63	Left PCoA	IV	IV	7	Yes	Yes	G
28	F/61	Right PCoA	III	IV	7	Yes	Yes	G
29	F/57	Left distal ACA	III	II	8	Yes	No	G
30	F/56	Left MCA bifurcation	IV	III	8	No	Yes	G

* SAH = subarachnoid hemorrhage; F = female; M = male; MCA = middle cerebral artery; ACoA = anterior communicating artery; PCoA = posteriorcommunicating artery; ICA = internal carotid artery; PICA = posterior inferior cerebellar artery; ACA = anterior cerebral artery; G = good outcome; MD = moderate disability; SD = severe disability; V = vegetative; D = dead; GOS = Glasgow outcome scale; mm = milimeters

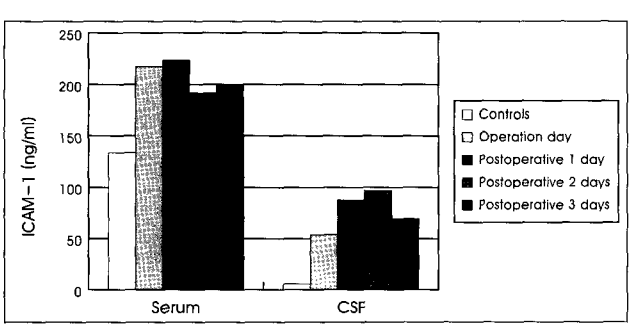

Fig. 1. Bar graphs showing the mean ICAM-1 levels in non-SAH controls and patients with aneurysmal SAH.

Correlation to clinical variables with CSF ICAM-1 level

This study demonstrated that the majority of clinical valuables has a interesting trend that ICAM-1 level was generally increased and highest at the second day after the operation and declined rapidly three days after the operation (Table 3).

Sex and age

CSF ICAM-1 level increased significantly during the first 3 sampling days according to sex and it was different from that observed in serum (Fig. 2). However, its difference was not statistically significant between men and women ($P>0.05$) (Table 3). In patients older than 65years, ICAM-1 levels increased gradually during the first 3 sampling days. These levels were higher than those in patients younger than 65years at all sampling times (Fig. 2). There seems to be a definite increasing tendency over 3days, but, the ICAM-1 levels between these two groups was not statistically different ($P>0.05$).

Hunt and Hess-grade

ICAM-1 levels were higher in poor grade patients than in good grade one. Even though ICAM-1levels increased gradually in good grade and poor grade patients during the first

Table 2. Demographic characteristics of control patients [a]

Patient no.	Sex/Age(yr)	Diagnosis	CSF sampling method	Serum ICAM-1 level	CSF ICAM-1 level
1	F/20	Herniated intervertebral disc	Lumbar puncture	117.56	0.001
2	M/72	Herniated intervertebral disc	Lumbar puncture	124.18	2.15
3	F/43	Unruptured aneurysm	Ventriculostomy	139.27	4.71
4	M/57	Unruptured aneurysm	Ventriculostomy	148.001	9.31

[a] F = female; M = male; CSF = cerebrospinal fluid; ICAM-1 = intercellular adhesion molecule-1

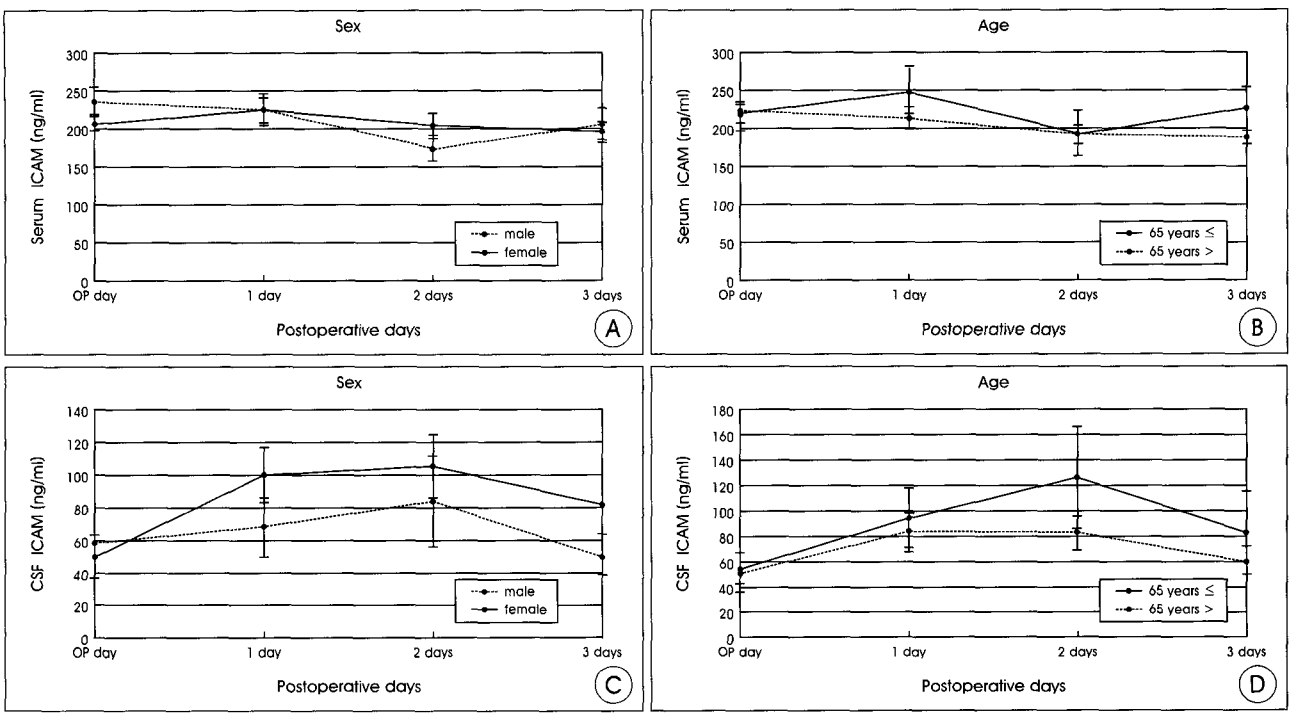

Fig. 2. Graphs depicting change of serum(A and B) and CSF(C and D) ICAM-1 levels over the entire 4-day sampling period according to sex and age.

3 sampling days compared to the ICAM-1 in serum (Fig. 3). At the operation day, the difference of ICAM-1 level between poor grade patients and good grade was stat-istically significant ($P<0.05$) (Table 3). On the other days, the ICAM-1 levels between two groups was not statistically different ($P>0.05$) (Table 3).

Fisher grade

ICAM-1 level was increased and highest at the second day after the operation and declined rapidly three days after the operation compared to the serum ICAM-1 levels (Fig. 3) (Table 3). In addition, ICAM-1 levels were higher in Fisher grade 3, 4 than in Fisher grade 1, 2patients. There seems to be a definite increasing tendency over 3days. However, this difference was not statistically significant different from serum ICAM-1 levels ($P>0.05$) (Table 3).

GOS

According to GOS score, ICAM-1 levels were markedly different in the aneurysmal SAH patients over the entire 4-day sampling period between favorable or unfavorable groups (Table 3). ICAM-1 levels were generally highest at the first day after the operation and declined rapidly (Fig. 4). This difference between these two groups was statistically significant ($P<0.05$) (Table 3).

Other factors

In regard to aneurysmal sac size and development of hydrocephalus, ICAM-1 levels were not markedly different in the aneurysmal SAH patients over the entire 4-day sampling period (Fig. 5) (Table 3).

And identically to those of serum, its difference between these two groups was not statistically significant ($P>0.05$) (Table 3).

Correlations to vasospasm with ICAM-1 level

Serum ICAM-1 levels were not different in patients with and without vasospasm over the entire sampling period (Fig. 6) (Table 3). And its difference was not statistically significant ($P>0.05$) (Table 4). However, CSF ICAM-1 level in patients suffering from vasospasm were always higher than in patients without vasospasm. There was a interesting

Table 3. Comparison of ICAM-1 concentration in serum and CSF in SAH patients with ruptured aneurysms [a]

Variables	Patient no.	Serum								CSF							
		OP day	*P* value**	POD 1day	*P* value	POD 2days	*P* value	POD 3days	*P* value	OP day	*P* value	POD 1day	*P* value	POD 2days	*P* value	POD 3days	*P* value
Age (years)																	
≥65	9	206.2	0.964	229.98	0.541	181.24	0.964	224.15	0.618	57.88	0.248	104.23	0.541	142.2	0.734	91.78	0.651
< 65	21	243.05		205.76		186.4		185.88		48.21		87.95		78.85		59.09	
sex																	
Male	12	243.01	0.299	212.94	0.611	157.58	0.397	205.4	0.657	49.98	0.783	61.31	0.162	82.96	0.236	42.39	0.169
Female	18	207.42		222.73		202.6		195.19		52.67		115.2		113.06		89.3	
Hunt Hess-grade																	
I, II, III	12	219.88	0.641	204.17	0.162	170.46	0.263	201.2	0.703	37.2	0.008***	82.3	0.086	86.36	0.117	44.39	0.06
IV, V	18	224.97		246.01		210.29		195.53		78.32		114.72		128.24		119.09	
Fisher grade																	
1, 2	13	208.46	0.025***	186.9	0.002***	168.2	0.016***	175.92	0.062	40.16	0.102	84.54	0.174	72.74	0.116	50.36	0.025
3, 4	17	241.46		266.68		209.18		234.3		68.74		107.31		143.43		100.8	
GOS																	
Good(≥4)	9	220.29	0.634	207.58	0.248	172.04	0.308	200.02	0.874	35.42	0.021***	77.86	0.067	82.18	0.029***	42.01	0.007***
Poor(3≥)	21	224.86		245.02		213.88		197.54		89.23		130.47		144.98		137.09	
Aneurysm sac size																	
< 1cm	21	232.25	0.575	231.75	0.714	187.43	0.788	216.66	0.251	45.93	0.942	89.49	0.864	102.46	0.696	62.54	0.625
≥ 1	9	207.6		208.87		192.28		178.14		70.73		99.75		95.35		78.59	
Hydrocephalus																	
Yes	19	240.08	0.148	245.91	0.059	175.71	0.368	223.5	0.313	26.47	0.334	95.43	0.861	117.49	0.776	75.49	0.895
No	11	215.08		212.04		196.7		193.41		69.68		92.32		90.14		63.01	
Vasospasm																	
Yes	17	239.11	0.116	241.53	0.207	214.42	0.512	203.01	0.536	57.15	0.047***	102.99	0.034***	100.46	0.062	89.35	0.107
No	13	208.21		205.64		160.68		206.15		50.15		81.33		99.94		43.45	

* OP day = operation day; POD = postoperative day; ICAM-1 = intercellular adhesion molecule; CSF = cerebrospinal fluid; SAH = subarachnoid hemorrhage; GOS = Glasgow outcome scale. ** Significance value were calculated by using the Mann-Whitney test. *** Probability value reaching the 0.05 level (statistically significant).

Table 4. Analysis of change of ICAM-1 levels according to development of vasospasm in SAH patients with ruptured aneurysms*

Vasospasm	Patient no.	Serum				CSF			
		OP day	POD 1 day	POD 2 days	POD 3 days	OP day	POD 1 day	POD 2 days	POD 3 days
Yes	17	239.11	241.53	214.42	203.01	57.15	102.99	100.46	89.35
P value**			0.551	0.109	0.065		0.038***	0.031***	0.045***
No	13	208.21	205.64	160.68	206.15	50.15	81.33	99.94	43.45
P value**			0.191	0.173	0.776		0.173	0.125	0.91

* SAH = subarachnoid hemorrhage; CSF = cerebrospinal fluid; OP day = operation day; POD = postoperative day. ** Significance value were calculated by using the Wilcoxon signed rank test. *** Probability value reaching the 0.05 level (statistically significant).

trend that ICAM-1 levels were generally highest at the first day after the operation and then declined (Fig. 6). The association between CSF ICAM-1 level and vasospasm was statistically significant ($P<0.05$) (Table 4).

Discussion

Cerebral vasospasm is a common and potentially incapacitating complication of aneurysmal SAH. Angiographic evidence of arterial spasm is seen in up to 70% of SAH patients, and clinical manifestations are witnessed in 20~30% of patients[24]. Despite maximal therapy, nearly 50% of patients with symptomatic vasospasm will develop infarction. 15% to 20% of patients will sustain a disabling stroke or die of progressive ischemia[35]. Although cerebral vasospasm after SAH has been the subject of substantial research efforts, the underlying pathogenic mechanisms remain obscure and no consistently efficacious therapies have as yet been identified and implemented in clinical practice[37].

Recently, research to identify the key pathogenic pathways of cerebral vasospasm was attempted and has suggested that the development of cerebral vasospasm is probably complex and multifactorial[3,14,23,44].

Among the potential causes of cerebral vasospasm, inflammation has been implicated in animal models of delayed arterial spasm[41] and in human stroke[28]. There has been a recent surge of studies examining many facets of the inflammatory response and expression of proinflammatory

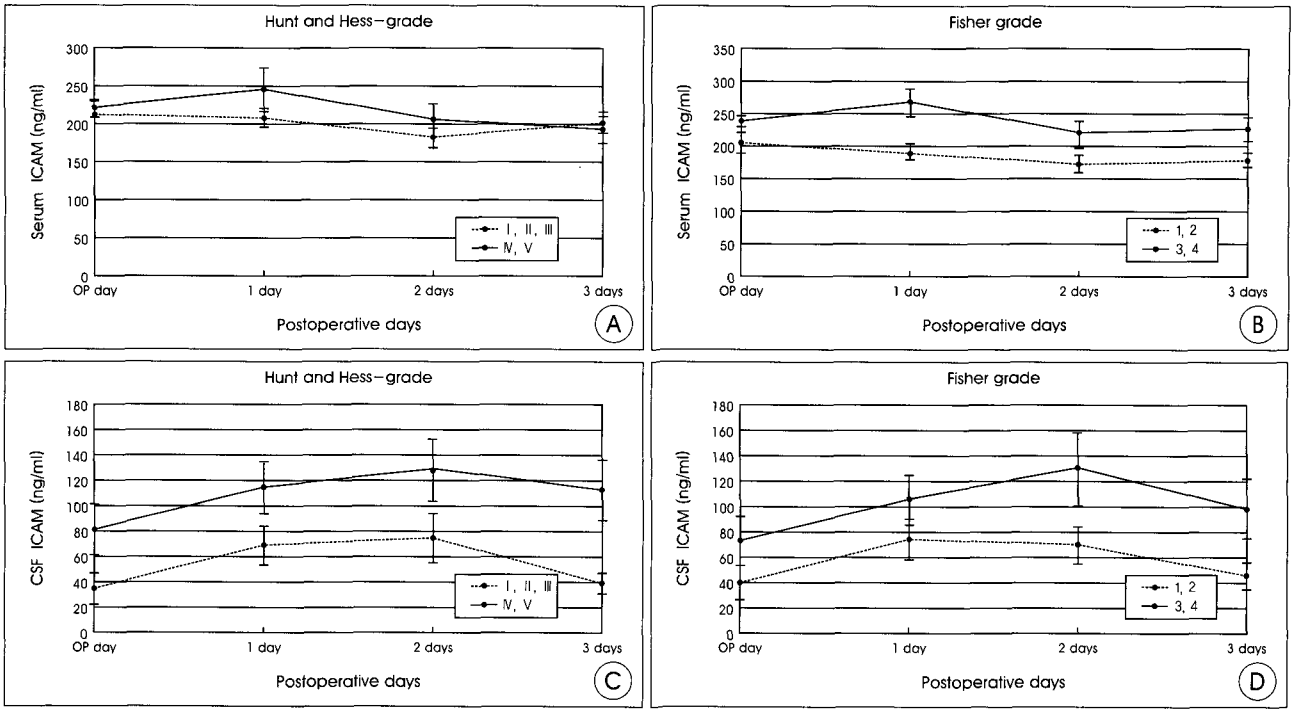

Fig. 3. Graphs depicting change of serum(A and B) and CSF(C and D) ICAM-1 levels over the entire 4-day sampling period according to Hunt and Hess-grades and Fisher grades.

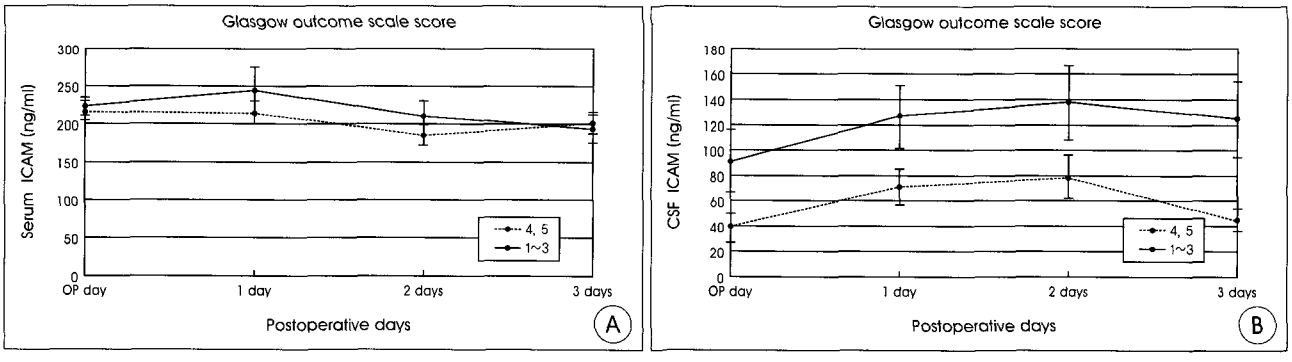

Fig. 4. Graphs depicting change of serum(A) and CSF(B) ICAM-1 levels over the entire 4-day sampling period according to Glasgow outcome scale at three month after aneurysmal operation.

markers accompanying experimental and clinical SAH[11,45].

The author hypothesized that cerebral vasospasm may be a complication as a result of inflammatory processes in subarachnoid space. To investigate possible correlations of adhesion molecule and cerebral vasospasm with aneurysmal SAH, the author measured the levels of adhesion molecule in the serum and CSF.

The term "adhesion molecule" encompasses a growing collection of related molecules that share the ability to influence immune and inflammatory reponses[45]. They differ in their mechanism of activation, their sites of activation, their site of expression and action, and their role in promoting the inflammatory response[46]. Although the role of most of these molecules in normal and pathological processes remains obscure, some putative functions have been postulated. The initial steps in the inflammatory pathway involve the activation of tissue macrophages and monocytes that release cytokines. Tumor necrotic factor and interleukin-1 are examples of cytokines involved in intiating the inflammatory response in the endothelial cells, promoting biosynthesis of adhesion molecules[11,13,14]. Among the adhesion molecules, such as intercellular adhesion molecule Type 1 (ICAM-1), the vascular cell adhesion molecule Type 1 (VCAM-1), and selectin, are strongly expressed after stroke and mediate inflammation via leukocyte activation and extravascular migration[17]. This process is charcterized by sequential interactions between adhesion molecules present on leukocytes and the endothelium. E-selectin establish neutrophil rolling on the surfaces of blood vessels, which initiates the adhesion casasade. The β, 2-integrin Mac-1

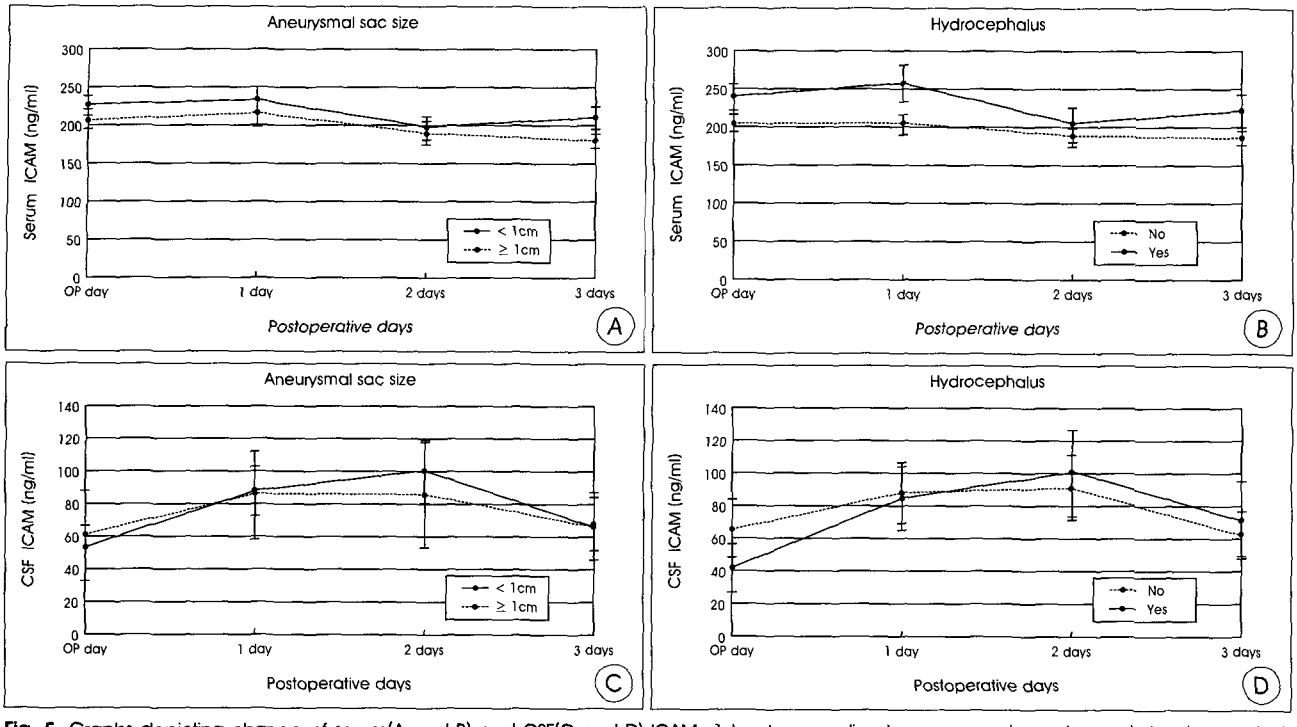

Fig. 5. Graphs depicting change of serum(A and B) and CSF(C and D) ICAM-1 levels according to aneurysmal sac size and development of hydrocephalus over the entire 4-day sampling period.

(CD11b/CD18) mediate firm adherence of neutrophils to the vessel wall by binding to its endothelial ligand, ICAM-1[25,32,39]. Level of the soluble isoform of VCAM-1 and ICAM-1 are increased in the serum and CSF of patients with subarachnoid hemorrhage, suggesting that an inflammatory process is active in these clinical models of brain injury[38,45]. Blockade or inactivation of these molecules has been effective in reducing brain injury in experimental ischemic brain injury models in rodents[4].

Experience with adhesion molecules in experimental models of SAH has been limited. Sills, et al.[50], demonstrated the expression of ICAM-1 in a rat femoral artery model of SAH. Using the same model, Oshiro, et al.[42], demonstrated the ability to block femoral vasospasm with antibodies to ICAM-1. Handa, et al.[18], found ICAM-1 immunostaining in the endothelium, media, and adventitia of the basilar artery after experimental SAH in rats. In addition, the use of anti-ICAM-1 monoclonal antibodies has been shown to reduce the incidence and severity of experimental vasospasm in both rats and rabbits[27]. Expression of the ICAM-1 gene has been shown to significantly rise in a canine model of SAH[1]. These animal findings suggest that ICAM-1 may be involved in the pathogenesis of vasos-pasm. However, experimental animal models of SAH are limited in their applicability of any results. For instance, animals do not generally develop cerebral ischemia in these models of experimental vasospasm[24].

Furthermore, the study of adhesion molecules has been limited in the serum, CSF ICAM-1 level in intracranial early aneurysmal SAH has rarely been studied[25,26]. Polin, et al.[45], demonstrated elevation of E-selectin, ICAM-1, and VCAM-1 levels in the CSF of patients after aneurysmal SAH. They suggested that the CSF levels of E-selectin, ICAM-1, and VCAM-1 may be related to the pathogenesis of cerebral vasospasm.

The author supposed that the CSF ICAM-1 level would be more sensitive than the levels in serum because the ruptured aneurysm is located in subarachnoid space which is filled with CSF. There are two possible explanations for the fact that ICAM-1 levels in the CSF may be more sensitive than in serum. First, with the endothelial damage and blood-brain barrier breakdown that occur in SAH, adhesion molecules can be introduced into the CSF directly[45]. Second, because the blood-brain barrier may become transiently permeable during cerebral ischemia, endothelial cell derived adhesion molecule isoforms can infiltrate into the subarachnoid space, which is the nearest space to the ruptured aneurysms[10,51].

The author also hypothesized that if cerebral vasospasm is related to the ascent of ICAM-1 in serum and CSF, the aneurysmal SAH patients with cerebral vasospasm should experience a significant rise in ICAM-1 in the posthemorrhagic period. Another possibility is that ICAM-1 levels in serum and CSF are elevated with a higher degree of elevation in patients with less favorable Hunt and Hessgrade at admission. To investigate these possibilities, this study focused on ICAM-

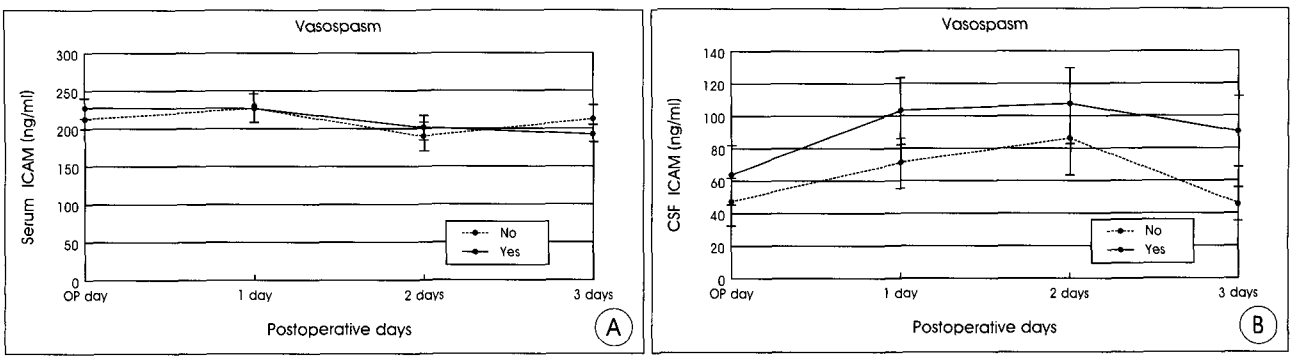

Fig. 6. Graphs depicting change of serum(A) and CSF(B) ICAM-1 levels according to development of vasospasm over the entire 4-day sampling period.

1 levels in CSF at various intervals after aneurysmal SAH and analyzed those with respect to changes in clinical variables of the patient.

The current lack of standardized data of the ICAM-1 in the CSF of aneurysmal SAH patients does not show correlation, between the neurological status of patients and the levels of adhesion molecules. The significance and mechanisms of change of ICAM-1 levels in CSF is unclear. However, the results in this study demonstrate a considerably intriguing trend in CSF. Over the entire study period, the CSF ICAM-1 levels were higher in older age patients, those with poor clinical status at admission and discharge, and patients with Fisher grades of 3, 4patients. Even though these were not statistically significant, however, there seems to be a definite increasing tendency over sampling period. Moreover, the CSF ICAM-1 level was always higher in patients with cerebral vasospasm compared with those without vasospasm. The association between CSF ICAM-1 level and vasospasm was statistically significant. The result of this study show that a correlation with the role of CSF ICAM-1 in the pathogenesis of cerebral vasospasm is suggested. And, the pronounced elevation of ICAM-1 in CSF in patients with aneurysmal SAH may assist in predicting the risk of vasospasm.

Currently, many studies on the role of ICAM-1 have also focused on the pathogenesis of cerebral ischemia/reperfusion injury[4,5,34]. Matsuo, et al.[34], have observed strong immunoreactivity for ICAM-1 between 1 and 24 hours after a 1-hour MCA occlusion in a rat model of ischemiareperfusion. Antibodies against ICAM-1 have been found to reduce infarct volumes in experimental stroke models[4]. Connolly, et al.[5], have shown that homozygous ICAM-1 knockout mice demonstrated a 3.7-fold reduction in infarct volume compared with control animals. Agents that inhibit the adherence of ICAM-1 to the cerebrovasculature may therefore prove to be valuable in the treatment of stroke[2,3,38].

Theoretically, therapies targeting ICAM-1 could be of value in the management of vasospasm after SAH for two reasons. First, blocking the function of ICAM-1 may provide cellular protection against ischemia[11,30]. Second, ICAM-1 may serve as an important component in the pathogenesis of vasospasm, acting to promote leukocyte migration across the vascular endothelium and initiating inflammation in the vascular wall that may contribute to vasospasm[3,13,32]. Clinical efforts to target this inflammatory component of vasospasm have focused on the general immuosuppressant cyclosporine, which has been shown to reduce vasospasm in the canine model[43]. but, has demonstrated mixed results in human trials[32]. The therapeutic value of using general immuosuppressant such as cyclosporine thus remains somewhat controversial[14,33].

There were two major limitations in this study. First of all, our sample size was too small. Further experimental studies will be required to assess whether ICAM-1 is involved in the pathogenesis of vasospasm or merely appear as byproducts, signaling that the process is taking place. Secondly, although ICAM-1 may induce delayed cerebral vasospasm, this study was carried out on the early stage of SAH. This was because this study focused on CSF, therefore, the risk of CNS infection had to be considered, and due to this consideration long-term cisternal drain insertion was impossible. Another point to be made is that through this study, we tried to identify any relationship between the change in ICAM-1 levels in the early stages of SAH and the actual prognosis of the patients.

However, the results from the present study cannot fully establish that these adhesion molecules mediate the vascular pathological processes associated with aneurysmal SAH. Further studies are required to determine whether these adhesion molecules have potential as diagnostic or therapeutic targets for management of cerebral vasospasm.

Conclusion

In conclusion, ICAM-1 is increased in CSF after early intracranial aneurysmal SAH and that this increase in ICAM-1 has correlation with cerebral vasospasm. Further investigation is warranted to determine 1) the exact role and concentration of ICAM-1 that induce vasospasm after aneurymal

SAH, and 2) whether adhesion molecules such as ICAM-1 may provide a novel therapeutic target in designing antivasospam therapy.

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