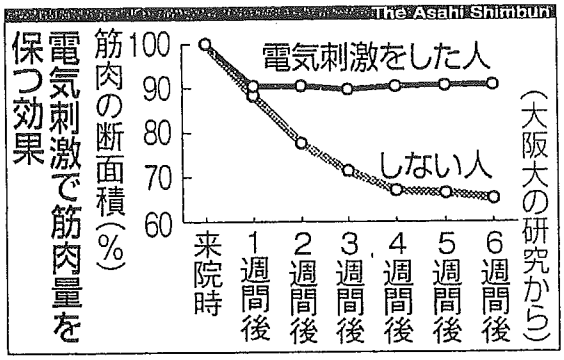
寝たきりの人 衰え予防

電気刺激で筋肉維持

病気や大けがで意識不明の寝たきり状態になった人の脚を電気で刺激すると、筋肉量が保たれることが、大阪大病院高度救命救急センターの研究で分かった。寝たきりになると急激に脚の筋肉が衰え、回復してもリハビリに長い時間がかかったり、車いす生活になったりする。この問題の解決に専門家も「朝報」と期待する。さいたま市で25日から開かれる日本神経外傷学会で発表される。

同センターの毛利智好医師と塩崎忠彦助手は頭の大けがなどで意識不明に陥った患者4人に、緊急救命治療が一段落した発病7日目から脚に電気刺激をした。



電気刺激で筋肉量を保つ効果

リハビリに朝報

大阪大病院へ発表

刺激は、筋肉を鍛える目的で使われる市販の器具を利用し、すね、ふくらはぎ、太ももの前後の計4カ所に30分施す内容で、1日に2回、入院中毎日続けた。強度は30～40ミリアンペアで、一流柔道選手がトレーニングに使う強度の5～6割にあたるという。

その結果、電気刺激をしない最初の7日間で筋肉の断面積は平均90%に減ったが、刺激を始めた後はそのまま90%前後を維持した。減り方に個人差はほとんどなかった。一方、比較するため電気刺激をしなかった6人は、筋肉の断面積が平均65%に減った。

塩崎助手は「この刺激器具は、介護家族も使える。意識が戻った後の社会復帰の可能性を広げるのに役立つだろう」と話す。

（中村通子）

国立身体障害者リハビリテーションセンター研究所の中澤公孝室長の話　筋肉の9割が保てれば、意識が戻った後の回復が早くなる。最新の研究では、筋肉への電気刺激は中枢神経にも好影響を与えることが分かってきており、大変期待できる手法だと思う。

図18

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻名	ページ	出版年
Inoue Y, et al.	Changes in cerebral blood flow from the acute to the chronic phase of severe head injury.	J. Neurotrauma	22	1411 – 1418	2005
Shiozaki T, et al.	Cerebrospinal fluid concentrations of anti-inflammatory mediators in early-phase severe traumatic brain injury.	Shock	23	406 – 410	2005
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Ibaraki M, et al.	PET measurements of CBF, OEF, and CMRO2 without arterial sampling in hyperacute ischemic stroke: method and error analysis.	Ann Nucl Med	18	35 – 44	2004
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Changes in Cerebral Blood Flow from the Acute to the Chronic Phase of Severe Head Injury

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ABSTRACT

We studied cerebral blood flow (CBF) in the transition from the acute to the chronic phase of severe head injury in order to determine patterns of change in relation to neurological outcome. We measured CBF with stable xenon-enhanced computed tomography (Xe-CT) in 20 consecutive patients at 1, 2, 3, 4, and 6 weeks after severe head injury, and analyzed the relation between the pattern of change in CBF and neurological outcome at 6 months after injury. CBF values were significantly lower in the brain-injured patients than in 14 healthy volunteers, except at 3 weeks after injury, when CBF increased in the patients to a value that did not differ significantly from that in the normal volunteers. We therefore focused on the change in CBF at 3 weeks after injury. We separated the 20 brain-injured patients into two subgroups, of which the first (subgroup A) consisted of nine patients whose CBF had returned to normal by week 3 post-injury, while the second (subgroup B) consisted of 11 patients whose CBF was subnormal at week 3 post-injury. CBF was significantly higher in subgroup A than in subgroup B at 2 weeks post-injury ($p < 0.05$). CBF in subgroup B remained significantly lower than that in subgroup A throughout the study period. At 6 months post-injury, subgroup A had a significantly better neurological outcome than did subgroup B ($p < 0.05$). We conclude that patients whose CBF returns to normal at 2–3 weeks following severe traumatic brain injury after being abnormally low in the acute phase of injury can be expected to achieve a good neurological outcome.

Key words: cerebral blood flow; neurological outcome; severe head injury; xenon-CT

INTRODUCTION

SEVERAL CLINICAL STUDIES have shown that severe traumatic brain injury often causes disturbances in cerebral blood flow (CBF) that lead to ischemia (Bouma et al., 1991; Enevoldsen et al., 1976) or hyperemia (Obris et al., 1984). Miller et al. (1985) proposed that cerebral ischemia is the single most important cause of brain injury secondary to severe head trauma. Histological evidence indicates that ischemic brain damage is common in most brain-injured patients who die (Miller, 1985). Bouma et al. (1992) reported that early global or regional ischemia after severe head injury was significantly associated with early mortality. Martin et al. (1997) charac-

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terized a cerebral hemodynamic phase during the first 2 weeks after severe head trauma in which reduced CBF is characterized by hypoperfusion, hyporemia, and vasospasm. However, most reports concerned with CBF in patients with severe injury have discussed only abnormalities in CBF in the initial 2 week post-injury period (Corte et al., 1997; Jaggi et al., 1990; Marion et al., 1991; Plougmann et al., 1994; Schröder et al., 1995), and have not made clear whether values reflecting CBF returned to normal in the chronic phases of injury.

The purpose of our study was to determine the pattern of change in CBF from the acute to the chronic phase in patients with severe traumatic brain injury, and to analyze the relation between CBF and neurological outcome. We were also interested in differences in CBF between normal volunteers and patients with severe head injury.

MATERIALS and METHODS

Patient Population

Between October 2000 and September 2002, 49 patients with severe head injury, whose Glasgow Coma Scale (GCS) score was 8 or less on admission, or in whom "talk and deteriorate" syndrome (Lobato et al., 1991) was confirmed, were admitted to the Trauma and Acute Critical Care Center of Osaka University Hospital. Of the 49 patients admitted, 29 did not meet the study criteria and were excluded; this group consisted of 15 patients over age 65 or under age 10 years, seven patients with uncontrollable intracranial hypertension, and seven patients with life-threatening injury to an organ other than the brain. This left 20 patients, consisting of 14 men and 6 women, ranging in age from 19 to 64 years (mean age, 32 years), who were included in the study. In each case, informed consent to participate was obtained from a patient's family member. Control subjects were 14 healthy adult male volunteers ranging in age from 25 to 45 years (mean age, 32 years).

Patient Management

All patients were initially intubated, artificially ventilated with a $PaCO_2$ of 30–35 mm Hg, and resuscitated with lactated Ringer's solution at 1.5–2.0 mL/kg/h. Intracranial pressure (ICP) was monitored with an intraventricular catheter or intraparenchymal sensor (Codman® Micro Sensor Basic Kit; Johnson & Johnson Co, Raynham, USA). In 16 patients, an ICP below 20 mm Hg was maintained with conventional treatments, consisting of cerebrospinal fluid (CSF) drainage, mild hyperventilation ($PaCO_2$ 30–35 mm Hg), and either continuous administration of propofol (4 mg/kg/h) or high-dose barbiturates according to published regimens (Sawada et al., 1982; Shiozaki et al., 1999). In four patients whose ICP remained above 20 mm Hg after high-dose barbiturate therapy, mild hypothermia (34°C) was induced according to our published regimens (Shiozaki et al., 1993, 1998). All treatments for reduction of ICP were completed within 1 week of injury.

Study Protocol

All patients were stabilized hemodynamically during the first week post-injury, and were examined for assessment of CBF at post-injury weeks 1 (7 ± 1 days), 2 (15 ± 1 days), 3 (21 ± 1 days), 4 (28 ± 1 days), and 6 (42 ± 1 days) with a CT scanner (Asteion-Multi TSX-021A; Toshiba, Tokyo, Japan) equipped with a stable xenon gas delivery system (AZ-725; Anzai Medical, Tokyo, Japan), and a matching CBF software package (AZ-7000W; Anzai Medical).

The technical details of CBF measurement with Xe-CT have been described elsewhere (Gur et al., 1982; Plougmann et al., 1994; Segawa et al., 1983; Schröder et al., 1995). Patients inhaled 30% ^{133}Xe gas (Xenon Cold®; Anzai Medical) mixed with 100% oxygen for 3 min, and then inhaled room air for the next 5 min to wash out the ^{133}Xe gas. Scans were obtained in six axial planes, each 5 mm thick and separated from one another by 10 mm, with the lowest plane chosen to include portions of the brain stem and top of the neocortex. Analytic computer software was then used to calculate CBF values. Average blood-flow values for both cerebral hemispheres, including the basal ganglia and excluding the Sylvian sulcus, were determined from tracer activity in regions of interest. End-expiratory ^{133}Xe and CO_2 concentrations, oxygen saturation, and electrocardiographic activity were monitored continuously during scanning. In addition, arterial blood gas levels and hematocrit (Hct) were determined before and after inhalation of ^{133}Xe. The CBF values were corrected to a standard $PaCO_2$ of 34 mm Hg, assuming a 3% increase in CBF for each 1 mm Hg increase in $PaCO_2$ (Bouma et al., 1991). We examined the 14 control subjects with the same stable Xe-CT technique used for the injured patients, and used the resulting data to estimate normal CBF values.

At the time of CBF measurement, we also evaluated clinical data including neurological function, blood pressure (BP), body temperature (BT), blood gas parameters, and Hct. During the 6-week observation period of the study, we evaluated neurological function with the Disability Rating Scale (DRS). The DRS was developed as a single instrument to provide quantative information for charting the progress of patients with severe head injury. The methodological details of the DRS have been described elsewhere (Rappaport et al., 1982).

Patient Outcome

All patients were discharged from the hospital at 6 weeks after injury. Outcome was assessed at 6 months after injury according to the patients' Glasgow Outcome Scale (GOS) scores (1 = death; 2 = vegetative state; 3 = severe disability; 4 = moderate disability; and 5 = mild or no disability) (Teasdale and Jennett, 1974). For statistical comparison, patients with a GOS score of 4 or 5 were classified as having a favorable outcome, and those with a GOS score of 1, 2, or 3 were classified as having an unfavorable outcome. Additionally, a follow-up interview was conducted at 6 months after injury with each patient or a family member, either through a clinic visit or by telephone.

Statistical Analysis

All values are expressed as mean ± standard deviation (SD). Changes in CBF values, DRS score, and other clinical parameters in both subgroups were analyzed by one-way analysis of variance (ANOVA) for repeated measures. When ANOVA indicated differences between the study subgroups, pairwise comparisons were made by calculating Dunnet's q statistic. We used the chi-square test to determine the relation between CBF values at week 3 and neurological outcome. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

Clinical characteristics of the 20 patients who met the study criteria are summarized in Table 1. A low ICP was defined as an ICP < 20 mm Hg achieved with conventional treatment, and a high ICP was defined as an ICP ≥ 20 mm Hg despite conventional treatment. Patients with a high ICP required mild hypothermia to control intracranial hypertension. Each of the 4 patients whose GCS score was above 8 at the time of admission showed deterioration in level of consciousness within 24 h after admission.

TABLE 1. PATIENT CHARACTERISTICS

Age (years)/ sex	*GCS on admission*	*CT findings*	*Additional injury*	*ICP*	*GOS result*	*Sub-group*
24/M	6	Contusion	—	Low[b]	GR	A
19/M	7	Traumatic SAH	Chest injury, leg fracture,	Low	GR	A
21/M	7	DAI/contusion	—	Low	MD	A
19/M	8	DAI	Arm fracture	Low	GR	A
22/M	8	SDH	—	Low	GR	A
23/M	8	Contusion	Chest injury	Low	GR	A
28/M	8	EDH	Leg fracture	Low	GR	A
30/F	12[a]	SDH EDH	—	High[c]	GR	A
45/M	15[a]	SDH	—	Low	GR	A
21/M	3	Traumatic ICH	—	High	PVS	B
56/F	3	SDH EDH	—	Low	PVS	B
25/M	4	SDH	—	High	MD	B
30/M	4	DAI	Leg fracture	Low	PVS	B
18/M	5	DAI	—	Low	SD	B
39/M	6	Contusion DAI	—	Low	SD	B
60/M	7	DAI	Chest injury	Low	PVS	B
64/F	8	Contusion	Arm fracture	Low	GR	B
64/F	8	SDH	Arm fracture	Low	SD	B
24/F	10[a]	SDH EDH	Pelvic fracture, arm fracture	High	SD	B
62/F	13[a]	SDH	Abdominal injury, arm fracture	Low	SD	B

[a]"Talk and deteriorate" syndrome.

[b]ICP was controlled at 20 mm Hg with conventional treatments.

[c]ICP was > 20 mm Hg, despite conventional treatments and induced mild hypothermia (34°C).

GCS, Glasgow coma scale; ICP, intracranial pressure; GOS, Glasgow Outcome Scale; DAI, diffuse axonal injury; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage; EDH, epidural hemorrhage; GR, good recovery; MD, moderate disability; SD, severe disability; PVS, persistent vegetative state.

Changes in CBF in Patients and Normal Volunteers

Figure 1 shows the changes in CBF in the 20 patients and the CBF values for the 14 healthy volunteers. A total of 100 CBF studies were done on the 20 patients during the 6-week observation period. Overall, CBF values in the head-injured patients were significantly below those of the healthy volunteers during each of the 6 weeks of the observation period (28.7 ± 10.5 vs. 40.6 ± 6.5 mL/100 g/min; $p < 0.05$), except for week 3 ($p < 0.05$).

Subgroup Analysis

Because CBF in the nine head-injured patients returned to normal by week 3 after injury, we divided them into two subgroups to follow their subsequent course. Subgroup A consisted of nine patients whose CBF was normal or above normal at week 3 after injury, while subgroup B consisted of 11 patients whose CBF was below normal at week 3 after injury. On admission, the two subgroups did not differ significantly with respect to clinical factors including age, GCS score, pupillary abnormalities, CT classification, or ICP (Table 2). DRS score and other clinical parameters such as BT, BP, blood-gas parameters, and Hct at the time of CBF measurement are shown in Table 3. The DRS scores of the two subgroups showed no significant difference during the 3 weeks after injury. However, beyond 4 weeks after injury, the DRS score of subgroup A was significantly lower than that of subgroup B (4 weeks: 8.9 ± 4.5 vs. 21.1 ± 5.9, 6 weeks: 5.1 ± 4.1 vs. 17.0 ± 8.5; $p < 0.05$). Other parameters did not differ for the two subgroups.

As shown in Figure 2, patterns of change in CBF differed significantly in the two subgroups ($p < 0.05$). In subgroup A, CBF values were lower than those of the normal volunteers at week 1 after injury, but had returned to normal by 2 weeks after injury, and at 3 weeks were higher than the values at 1 week post-injury ($p < 0.05$). In subgroup B, CBF values were lower than those of the normal volunteers throughout the 6-week observation pe-

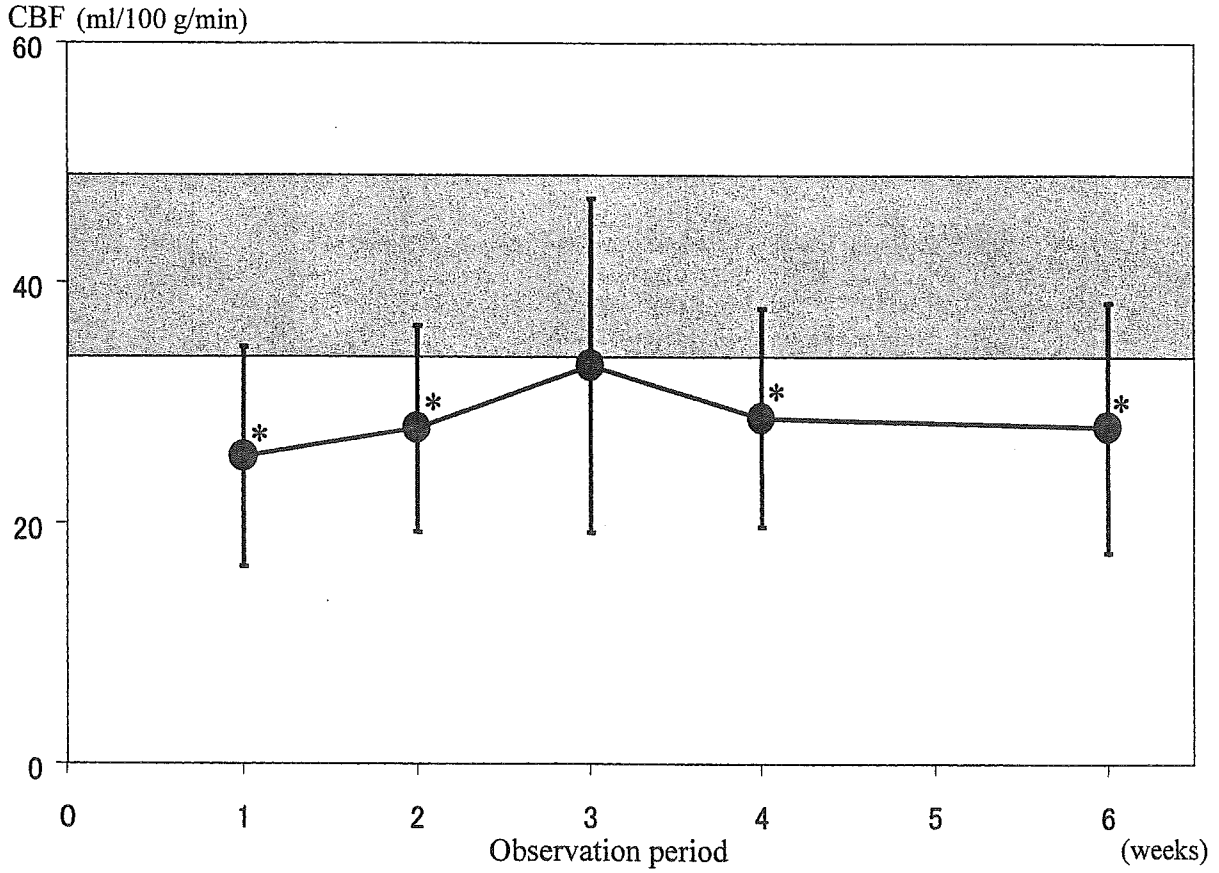

FIG. 1. Cerebral blood flow (CBF) change in the 20 head-injury patients during the 6-week observation period. Data are shown as mean ± SD. The gray zone represents the normal range of CBF, seen in the 14 healthy volunteers. Statistical analysis of each week's CBF value was done with Student's *t*-test. *$p < 0.05$ versus normal volunteers.

TABLE 2. CLINICAL CHARACTERISTICS OF SUBGROUPS A AND B

	Subgroup A, n = *9*	*Subgroup B,* n = *11*
Sex (M/F)	8/1	6/5
Mean age (years)	26 ± 8	42 ± 19
Admission GCS score[a]	9 ± 2	7 ± 3
Pupillary abnormalities on admission	4	6
CT classification[b]		
I	3	1
II	3	3
III	2	2
IV	0	0
Evaculated mass lesion	1	5
Nonevaculated mass lesion	0	0
High ICP	1	3
Outcome		
GR/MD	9	2
SD/V/D	0	9

[a]"Talk and deteriorate" syndrome: two patients in subgroup A and two patients in subgroup B.

[b]Classification of Traumatic Coma Data Bank (Marshall et al., 1992).

GR, good recovery; MD, moderate disability; SD, severe disability; V, vegetative state; D, death.

riod. CBF values in subgroup A were significantly higher than those in subgroup B at week 2 after injury ($p < 0.05$).

Clinical Outcome

In subgroup A, 6-month outcomes after injury consisted of good recovery in eight patients, and moderate disability in one patient. In subgroup B, 6-month outcomes after injury consisted of good recovery in one patient, moderate disability in one patient, severe disability in five patients, and a persistent vegetative state in four patients. The neurological outcome in subgroup A at 6 months after injury was significantly better than that in subgroup B ($p < 0.05$).

DISCUSSION

We noticed two distinct patterns of change in CBF in patients with severe traumatic brain injury during the first 6 weeks after injury. In the first pattern, seen in subgroup A of our brain-injured patients, CBF values returned to normal at week 3 after injury, while in the second pattern, seen in subgroup B, CBF values remained low throughout the 6 weeks after injury. Patients in subgroup A showed significantly better neurological outcomes than those in subgroup B.

Martin et al. (1997) reported time-dependent changes in ^{133}Xe-clearance–determined CBF in patients with severe closed head injury during the first 2 weeks after injury. They described the changes in CBF as occurring in three discrete phases: hypoperfusion in the first 24 h, hyperemia on days 1–3, and vasospasm on days 4–15 post-injury. As far as we know, however, Martin and colleagues did not observe changes in CBF beyond the initial 2 weeks after injury. We therefore measured CBF in our head-injured patients at weeks 1, 2, 3, 4, and 6 after injury, and investigated the relation between change in CBF and neurological outcome. Because CBF was influenced by various interventional procedures during the first week after admission, such as the use of sedative drugs, control of BT, and surgery, we began our study at 1 week after injury, to exclude the influence of these procedures.

Our study clearly showed that CBF in patients with severe head injury was significantly below that of healthy subjects except at week 3 after injury. Martin et al. (1997) hypothesized that CBF recovered gradually beyond 2 weeks after injury as a result of decreased vasospasm. Several other studies have also reported that vasospasm may be an important determinant of outcome in severe head injury (Pasqualin et al., 1984; Martin et al., 1995). However, our study found two characteristic patterns of change in CBF during the initial 6 weeks after injury. The first pattern was that seen in subgroup A, in which CBF was below normal at week 1 after injury, increased at week 2 , reached a peak value at week 3, and remained normal thereafter. In the second pattern, seen in subgroup B, CBF remained subnormal throughout the entire 6-week period of observation after injury. To explain these two patterns of change in CBF, we hypothesize that the low CBF of subgroup B is linked to a reduction in cerebral metabolism despite a decrease in vasospasm. To clarify the relation between cerebral blood supply and cerebral metabolic demand from the acute to the chronic phase of severe head injury, future studies will require the measurement of cerebral oxygen and glucose metabolism with the Xe-CT, together with three-dimensional CT angiography, analysis of SjO_2, and [^{18}F]fluorodeoxyglucose–positron emission tomography (FDG-PET).

A further important point in our study was that subgroup A had a significantly better neurological outcome than did subgroup B. By 2 weeks after injury, almost all of our patients had lost consciousness, and their DRS scores were quite high. However, beyond 4 weeks post-injury, the DRS scores of subgroup A had recovered to a degree that they were significantly lower than those for subgroup B, and patient consciousness in subgroup A re-

TABLE 3. CLINICAL DATA FOR SUBGROUPS A AND B

	Week 1		*Week 2*		*Week 3*		*Week 4*		*Week 6*	
Group	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*
DRS	24.2 ± 3.5	26.5 ± 2.6	19.9 ± 2.7	22.8 ± 4.9	17.8 ± 4.1	22.1 ± 5.6	8.9 ± 4.5*	21.2 ± 5.9	5.1 ± 4.1*	17.0 ± 8.5
BT (°C)	37.4 ± 0.6	37.5 ± 0.4	37.4 ± 0.4	37.2 ± 1.2	37.3 ± 0.6	37.4 ± 0.2	37.5 ± 0.7	36.9 ± 0.5	37.3 ± 0.2	37.3 ± 0.2
Bp sys (mm Hg)	135 ± 10	167 ± 15	128 ± 12	139 ± 19	118 ± 4	135 ± 14	122 ± 13	127 ± 13	124 ± 13	122 ± 12
Bp dia (mm Hg)	72 ± 7	87 ± 14	71 ± 12	75 ± 12	68 ± 8	74 ± 10	57 ± 12	71 ± 12	69 ± 15	73 ± 13
PaO_2 (mm Hg)	111 ± 19	113 ± 19	109 ± 12	101 ± 14	87 ± 31	97 ± 17	104 ± 9	92 ± 13	102 ± 11	97 ± 6
$PaCO_2$ (mm Hg)	36 ± 3	36 ± 4	39 ± 3	37 ± 5	38 ± 5	39 ± 3	38 ± 4	38 ± 4	39 ± 4	41 ± 2
pH	7.445 ± 0.21	7.448 ± 0.17	7.458 ± 0.02	7.446 ± 0.31	7.450 ± 0.09	7.441 ± 0.20	7.463 ± 0.180	7.457 ± 0.19	7.472 ± 0.19	7.438 ± 0.09
BE (mEq/L)	0.9 ± 1.2	0.7 ± 2.0	3.3 ± 1.8	1.8 ± 1.6	2.3 ± 3.4	2.5 ± 1.6	3.3 ± 1.7	2.8 ± 1.8	1.5 ± 0.9	2.9 ± 0.7
Hct (%)	31.2 ± 6.9	30.3 ± 4.7	29.8 ± 6.1	29.1 ± 2.4	27.7 ± 1.7	29.9 ± 4.5	34 ± 3	32 ± 2	34.5 ± 1.6	36.3 ± 1.7

*Group A versus group B, $p < 0.05$.

The Disability Rating Scale (DRS) is an ordinal scale that ranges from 0 to 30, with 0 rated as no disability and 30 rated as death.

BT, body temperature; Bp sys, systolic blood pressure; Bp dia, diastolic blood pressure; Hct, hematocrit.

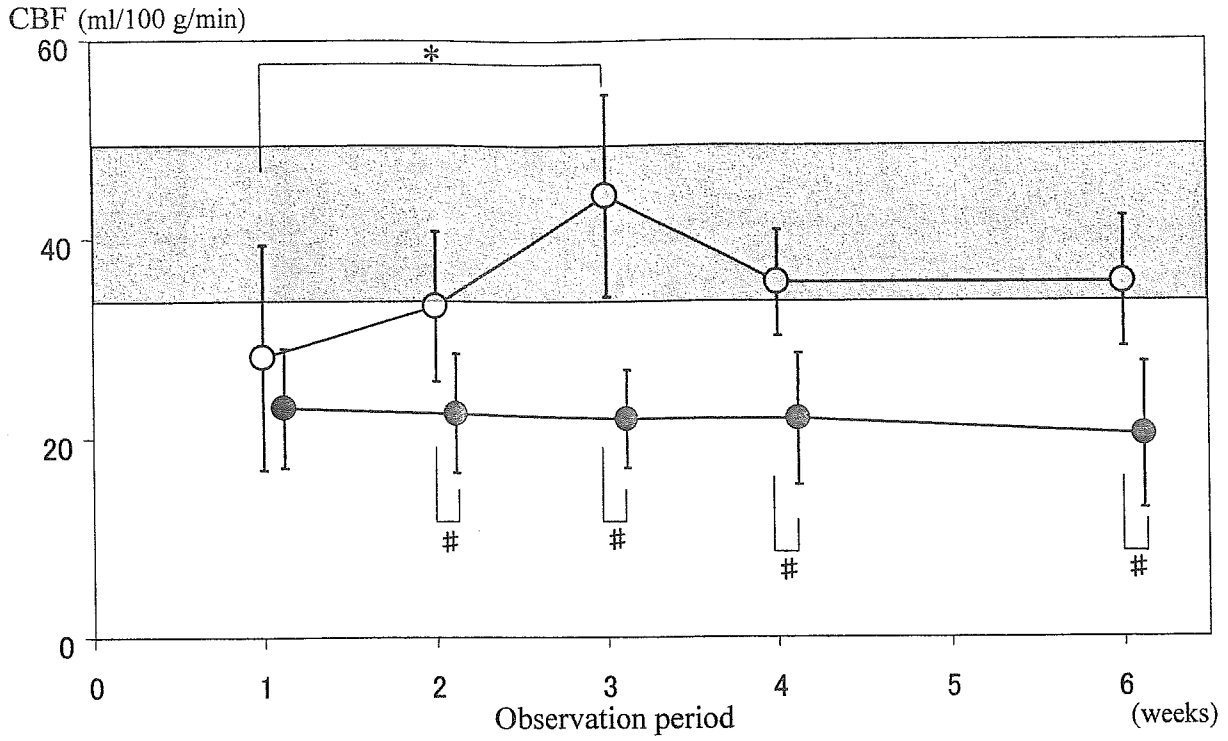

FIG. 2. Cerebral blood flow (CBF) patterns in subgroups A and B during the 6-week observation period. Data are shown as mean ± SD. Open circles, CBF data for subgroup A; closed circles, CBF data for subgroup B. The gray zone represents the normal range of CBF, seen in the 14 healthy volunteers. Statistical analysis was done by calculating Dunnet's q statistic. $*p < 0.05$ for CBF at week 1 versus week 3 after injury; $\#p < 0.05$, subgroup A versus subgroup B.

vealed improvement (Table 3). Even at 2 weeks post injury, the CBF in subgroup A was significantly higher than that in subgroup B. Because the two subgroups' neurological states at 2 or 3 weeks after injury were similar, we conclude that patients with severe head injury whose CBF returns to normal within 3 weeks after injury are highly likely to regain consciousness, and hypothesize that CBF at 2 or 3 weeks after injury may be one of the most useful factors for predicting neurological outcome following severe head injury.

Our study had several limitations. Because our study population was small, our study groupings may have produced some biases. For example, the number of patients over 50 years old was 0 (0%) in subgroup A and 5 (45%) in subgroup B; the number of patients with GCS scores under 5 on admission was 1 (11%) in subgroup A and 5 (45%) in subgroup B; the number of patients treated with mild hypothermia for a high ICP was 3 (27%) in subgroup A and 0 (0%) in subgroup B; and the number of patients who underwent evacuation of mass lesions was 1 (11%) in subgroup A and 5 (45%) in subgroup B, although none of these differences was statistically significant. Nevertheless, we cannot rule out the possibility that the low CBF in subgroup B may have been a natural consequence of early intracranial pathology. Obviously, further study of the effects of severe head injury is needed, with an important goal of this research seeking to determine whether therapeutic procedures for increasing CBF can improve neurological outcome in patients whose CBF remains subnormal beyond 3 weeks post-injury.

In sum, we measured CBF with Xe-CT in normal volunteers and patients with severe head injury, and observed two patterns of change in CBF during 6-week period post-injury. The first pattern was a subnormal CBF at 1 week after injury, followed by an increase at 2 weeks, with a peak value at 3 weeks, and a sustained normal level beyond 3 weeks. The second pattern was a low CBF throughout the initial 6 weeks following injury. A good neurological outcome at 6 months after injury was associated with the first of these two CBF patterns.

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CEREBROSPINAL FLUID CONCENTRATIONS OF ANTI-INFLAMMATORY MEDIATORS IN EARLY-PHASE SEVERE TRAUMATIC BRAIN INJURY

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ABSTRACT—In our previous study of patients with early-phase severe traumatic brain injury (TBI), the anti-inflammatory interleukin (IL)-10 concentration was lower in cerebrospinal fluid (CSF) than in serum, whereas proinflammatory IL-1β and tumor necrosis factor (TNF)-α concentrations were higher in CSF than in serum. To clarify the influence of additional injury on this disproportion between proinflammatory and anti-inflammatory mediators, we compared their CSF and serum concentrations in patients with severe TBI with and without additional injury. All 35 study patients (18 with and 17 without additional injury) had a Glasgow Coma Scale score of 8 or less upon admission. With the exception of additional injury, clinical characteristics did not differ significantly between groups. CSF and serum concentrations of two proinflammatory mediators (IL-1β and TNF-α,) and three anti-inflammatory mediators (IL-1 receptor antagonist [IL-1ra], soluble TNF receptor-I [sTNFr-I], and IL-10) were measured and compared at 6 h after injury. CSF concentrations of proinflammatory mediators were much higher than the corresponding serum concentrations in both patient groups ($P < 0.001$). In contrast, serum concentrations of anti-inflammatory mediators were much higher than the paired CSF concentrations in patients with additional injury ($P < 0.001$), but serum concentrations were lower than or equal to the corresponding CSF concentrations in patients without additional injury. CSF concentrations of IL-1β, IL-1ra, sTNFr-I, and IL-10 were significantly higher ($P < 0.01$ for all) in patients with high intracranial pressure (ICP; n = 11) than in patients with low ICP (n = 24), and were also significantly higher ($P < 0.05$ for all) in patients with an unfavorable outcome (n = 14) than in patients with a favorable outcome (n = 21). These findings indicate that increased serum concentrations of anti-inflammatory mediators after severe TBI are mainly due to additional extracranial injury. We conclude that anti-inflammatory mediators in CSF may be useful indicators of the severity of brain damage in terms of ICP as well as overall prognosis of patients with severe TBI.

KEYWORDS—IL-1ra, sTNFr-I, IL-10, cerebrospinal fluid, head injury

INTRODUCTION

We have reported that concentrations of proinflammatory interleukin (IL)-1β and tumor necrosis factor (TNF)-α were higher in cerebrospinal fluid (CSF) than in serum of patients with early-phase severe traumatic brain injury (TBI), whereas concentrations of anti-inflammatory IL-10 were lower in CSF than in serum (1). This notable disproportion between proinflammatory mediators and anti-inflammatory mediators after severe TBI is consistent with the observations of Maier et al. (2). Partrick et al. (3) reported that serum concentrations of anti-inflammatory mediators (IL-1 receptor antagonist [IL-1ra] and soluble TNF receptor-I [sTNFr-I]) were dramatically increased in trauma patients within 12 h after the event (3). Shimonkevitz et al. (4) also reported that IL-10 was found in peripheral blood immediately after TBI. Therefore, we hypothesized that additional extracranial injury may be involved in the disproportion in mediator concentrations. To test our hypothesis, we examined CSF and serum concentrations of anti-inflammatory mediators and proinflammatory mediators in patients with severe TBI with or without additional injury. For the purpose of this study, we selected two proinflammatory mediators (IL-1β and TNF-α) and three anti-inflammatory mediators (IL-1ra, sTNFr-I, and IL-10) that have been analyzed in the clinical setting (5–9). In this study, we also assessed the relation of CSF anti-inflammatory mediators to intracranial pressure (ICP) and prognosis of patients with severe TBI.

MATERIALS AND METHODS

Patient population

During the period of 1998 to 2002, a total of 73 patients with a Glasgow Coma Scale (GCS) (10) score of 8 or less were admitted to the Department of Traumatology, Osaka University Graduate School of Medicine. Patients less than 10 years of age were excluded from this study. Eight patients who suffered severe life-threatening injury to organs other than the brain were also excluded from this study. CSF or serum samples could not be obtained from 30 of the remaining 65 patients, therefore, these 30 were excluded. Thus, 35 patients were included in this study: 17 without additional extracranial injury and 18 with additional extracranial injury. Of the 35 patients, 26 were men and 9 were women. Their age averaged 39 years and ranged from 14 to 77 years. No patient had pre-existing neurological disease. Informed consent for participation in the study was obtained from an appropriate member of each patient's family.

Eight patients with additional extracranial injury and eight patients without additional extracranial injury were overlapped in our previous study (1).

Patient management

After intubation, all patients were subjected to continuous mild hyperventilation, which was induced with $PaCO_2$ between 30 and 35 mmHg, and all received high-dose barbiturates with mild fluid restriction (1-2 mL/kg/h). When cerebral perfusion pressure (mean arterial blood pressure minus ICP) dropped to less than 60 mmHg, patients were given adequate amounts of albumin. Colloidal fluids or dopamine

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(3-5 μg/kg/min continuous infusion) was administered as needed to maintain urine output greater than 0.5 mL/kg/h. No corticosteroid or mannitol was administered during the study. Immediately after initial resuscitation, all patients underwent computed tomography (CT) scanning of the head. Subsequently, an intraventricular catheter was placed in each patient. The catheter allowed continuous monitoring of ICP and intracranial temperature. There was no evidence of complications, such as intracranial hemorrhage or infection, due to insertion of the intraventricular catheter. Intracranial mass lesions associated with midline displacement greater than 5 mm were surgically removed when necessary. Intracranial hypertension was managed initially in all patients by conventional ICP reduction therapy, such as mild hyperventilation, mild fluid restriction, high-dose barbiturates, and/or CSF drainage. In patients with ICP at or above 20 mmHg and those who were unresponsive to conventional therapy, mild hypothermia (34°C) was induced by surface cooling with a circulating water blanket placed above and below the patient. Intracranial temperature was controlled according to our previously published protocol (11). Control of ICP was achieved in 24 of the 35 patients, but not in the remaining 11. Patients with low ICP were assigned randomly to mild hypothermia (12 patients) or normothermia (12 patients). After randomization, patients assigned to mild hypothermia were subjected to mild hypothermia (intracranial temperature of 34°C) as quickly as possible, and patients assigned to normothermia were maintained under normothermic conditions (intracranial temperature of 37°C). Mild hypothermia was started 1.9 ± 0.5 h after injury, and body temperature reached 34°C 6.0 ± 0.5 h after injury. Mild hypothermia was continued for 48 h, and patients were rewarmed at 1°C/day for 3 days. Normothermia (37°C) was maintained for 5 days.

CSF and serum analysis

CSF samples were drawn from the intraventricular catheter, and blood samples were drawn from an arterial line simultaneously 6 h after injury. The CSF samples were centrifuged to remove cellular debris, and the supernatant was immediately frozen at −80°C and stored until analysis. Serum samples were prepared from the blood samples and were stored at −80°C until analysis. IL-1β, TNF-α, IL-1ra, sTNFr-I, and IL-10 concentrations in CSF and serum were analyzed by enzyme-linked immunosorbent assay with commercially available kits (R&D Systems, Minneapolis, MN). The minimum detectable mediator concentrations were IL-1β, 1 pg/mL; TNF-α, 4.4 pg/mL; IL-1ra, 14 pg/mL; sTNFr-I, 3.0 pg/mL; and IL-10, 3.9 pg/mL. For statistical analysis, minimum detection-level values were used for mediator concentrations below the minimum detectable levels.

Injury severity score

Injury severity score (ISS) is calculated using the standard method of squaring the three 1990 Abbreviated Injury Scale score values for the three body regions most severely injured (12, 13).

Patient outcomes

Patient outcome was assessed 6 months after injury on the basis of the Glasgow Outcome Scale (GOS) (14) in which death is scored as 1, vegetative state as 2, severe disability as 3, moderate disability as 4, and good recovery as 5. For statistical comparison, the outcome of patients with a score of 4 or 5 was considered favorable and the outcome of patients with a score of 1, 2, or 3 was considered unfavorable. Surviving patients participated in follow-up interviews by telephone or in person at the clinic.

Statistical analysis

All values are expressed as mean ± SEM unless otherwise specified. Statistical analyses were performed with Stat-View computer software (version 5.0) and included Mann-Whitney *U* test, chi-square test, or Fisher exact test. Relations between variables were assessed by Pearson's correlation coefficient. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Patient characteristics

Clinical characteristics of patients in the two groups are summarized in Table 1. The groups did not differ significantly with respect to prognostic factors on admission such as patient age, GCS score, pupil abnormalities, or CT classification. ISS in patients with additional extracranial injury was significantly higher than that in patients without additional extracranial injury ($P < 0.001$).

Of the 35 patients, 12 made up the "patients with low ICP treated under normothermia," 12 made up the "patients with low ICP treated under mild hypothermia," and 11 made up the "patients with high ICP." All patients with high ICP were treated under mild hypothermia; none were treated under normothermia. The number of patients treated under each condition did not differ significantly between patients with and without additional injury (Table 1).

Mediator concentrations in patients without additional extracranial injury

CSF and serum concentrations of all substances measured in patients without additional extracranial injury (n = 17) are shown in Figure 1. CSF concentrations of the two proinflammatory mediators (IL-1β, 10.9 ± 2.3 pg/mL; TNF-α, 18.4 ± 4.9 pg/mL) were significantly higher than the corresponding serum concentrations (IL-1β, 1.6 ± 0.2 pg/mL; TNF-α, 5.0 ± 0.4 pg/mL; $P < 0.001$). As to the three anti-inflammatory mediators, CSF concentrations of sTNFr-I (984 ± 137 pg/mL) and IL-10 (13.5 ± 4.3 pg/mL) were almost equal to the corresponding serum concentrations (sTNFr-I, 878 ± 107 pg/mL IL-10, 13.6 ± 3.1 pg/mL). CSF concentrations of IL-1ra (1670 ± 377 pg/mL) was significantly higher than the corresponding serum concentrations (621 ± 114 pg/mL; $P = 0.034$).

Mediator concentrations in patients without additional extracranial injury

CSF and serum concentrations of all substances measured in patients with additional extracranial injury (n = 18) are shown in Figure 2. CSF concentrations of the two proinflammatory mediators (IL-1β, 9.9 ± 1.9 pg/mL; TNF-α, 16.6 ± 3.5 pg/mL) were significantly higher than the corresponding serum concentrations (IL-1β, 1.5 ± 0.2 pg/mL; TNF-α, 5.1 ± 0.4 pg/mL; $P < 0.001$). Unlike patients without additional extracranial injury, serum concentrations of the three anti-inflammatory mediators (IL-1ra, 26,861 ± 10,354 pg/mL; sTNFr-I, 2590 ± 356 pg/mL; and IL-10, 69.3 ± 20.2 pg/mL) were markedly higher than the corresponding CSF concentrations (IL-1ra, 1920 ± 381 pg/mL; sTNFr-I; 831 ± 144 pg/mL; and IL-10, 12.9 ± 2.5 pg/mL) in patients with additional injury ($P < 0.001$).

Mediator concentrations in relation to extracranial additional injury

Serum concentrations of the three anti-inflammatory mediators (IL-1ra, 26,861 ± 10,354 pg/mL; sTNFr-I, 2590 ± 356 pg/mL; and IL-10, 69.3 ± 20.2 pg/mL) in patients with additional extracranial injury were several times higher than those in patients without additional extracranial injury (IL-1ra, 621 ± 114 pg/mL; sTNFr-I, 878 ± 107 pg/mL; and IL-10, 13.6 ± 3.1 pg/mL; $P < 0.001$). There were no significant differences in CSF concentrations of the two proinflammatory mediators, serum concentrations of the two proinflammatory mediators, or CSF concentrations of the three anti-inflammatory mediators between the two groups.

Serum concentrations of anti-inflammatory mediators in relation to ISS

Significant positive correlation was found between ISS and serum sTNFr-I concentrations ($r^2 = 0.365$, $P < 0.001$). No significant correlation was found between ISS and serum IL-1ra

TABLE 1. Clinical characteristics of the two study groups

	Patients without extracranial additional injuries	Patients with extracranial additional injuries	*P* value*
No. of patients	17	18	
Age (yrs)	41 ± 5	37 ± 4	0.531
Sex ratio (M/F)	12/5	14/4	0.711
GCS on admission	5.4 ± 0.4	5.9 ± 0.4	0.409
Pupil abnormalities on admission†	10	13	0.489
Hypoxia on admission‡	7	9	0.738
Hypotension on admission§	3	6	0.443
CT classification‖			0.700
diffuse injury 1	1	1	
diffuse injury 2	5	8	
diffuse injury 3	0	1	
diffuse injury 4	1	1	
evacuated mass lesion	10	7	
nonevacuated mass lesion	0	0	
Treatment assignment			0.694
patients with low ICP treated under normothermia¶	5	7	
patients with low ICP treated under mild hypothermia¶	7	5	
patients with high ICP¶	5	6	
Additional injury**			
chest injury	0	9	
abdominal injury	0	4	
pelvic or leg fracture	0	8	
arm fracture	0	4	
Injury severity score††	22.5 ± 0.2	41.7 ± 0.6	<0.001
Outcome			
favorable/unfavorable	11/6	10/8	0.733

Numbers represent number of patients unless otherwise indicated.
Values are expressed as mean ± SE.
†Pupil abnormalities were defined as abnormalities in size and/or reaction to light in one or both pupils.
‡Hypoxia was defined as PaO_2 less than 60 mmHg.
§Hypotension was defined as a sustained fall in systolic blood pressure to 100 mmHg.
‖Categorized according to the classification of Marshall, et al. (J Neurosurg 75:S14–S20, 1991).
¶low 1CP: patient's ICP was maintained below 20 mmHg by conventional treatments.
‡‡High ICP: patient's ICP could not be lowered to below 20 mmHg despite conventional treatments. All patients with high ICP were treated under mild hypothermia.
**Overlapped in some patients.
††Injury Severity Score is calculated using the standard method of squaring the three 1990 Abbreviated Injury Scale score values for the three body regions most severely injured (12, 13).
*Mann-Whitney *U*-test was used for the comparison of age, GCS on admission, and Injury Severity Score. Fisher exact test was used for the comparison of sex ratio, the incidence of pupil abnormalities on admission, hypoxia on admission, and hypotension on admission, and outcome. Chi-square test was used for the comparison of CT classification and treatment assignment.

concentrations ($r^2 = 0.001$) or between ISS and serum IL-10 concentrations ($r^2 = 0.050$).

Correlation of GCS score with CSF concentrations of mediators

Because CSF concentrations of both proinflammatory mediators and anti-inflammatory mediators did not differ between the two groups, we examined correlation of GCS score on admission with CSF concentrations of mediators in all 35 patients regardless of the existence of additional extracranial injury. No significant correlation was found between CSF concentrations of any mediator and a patient's GCS score on admission.

Correlation of ICP with CSF concentrations of mediators

The CSF concentrations of all substances in patients with high ICP (n = 11) and those with low ICP (n = 24) are shown in Table 2. The CSF concentrations of IL-1β, IL-1ra, sTNFr-I, and IL-10 were significantly higher in patients with high ICP than those with low ICP ($P = 0.002$, $P = 0.006$, $P = 0.009$, and $P = 0.009$, respectively). However, the CSF concentrations of TNF-α did not differ between patients with high ICP and those with low ICP.

Correlation between CSF concentrations of mediators and outcome

At 6 months after TBI, outcome was favorable for 21 patients, but were unfavorable for 14 patients (Table 3). The CSF concentrations of IL-1β, IL-1ra, sTNFr-I, and IL-10 were significantly higher in patients with an unfavorable outcome than in patients with a favorable outcome ($P = 0.006$, $P = 0.009$, $P = 0.003$, and $P = 0.012$, respectively). However, the CSF concentrations of TNF-α did not differ between patients with an unfavorable outcome and those with a favorable outcome.

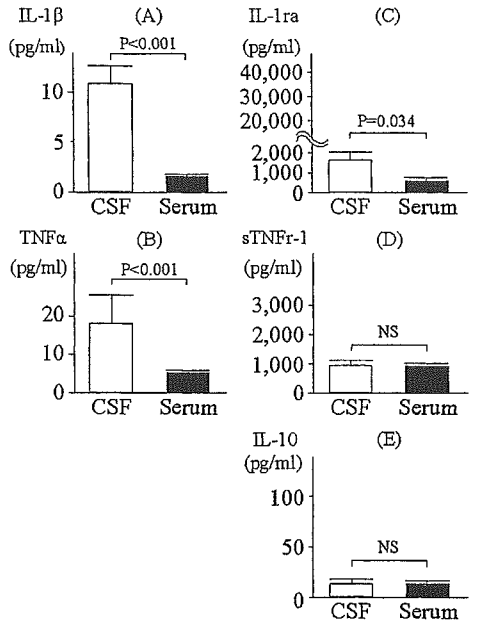

FIG. 1. **Graphs showing CSF and serum concentrations for all substances measured in patients without extracranial additional injury (n = 17).** Open bar, CSF samples. Closed bar, serum samples. Data are expressed as mean ± SEM.

DISCUSSION

This study was designed to answer the following two questions: Is the increase of serum concentrations of anti-inflammatory mediators related to the existence of additional extracranial injury? Is the CSF concentrations of anti-inflammatory mediators related to ICP and prognosis of patients with severe TBI?

In the present study, serum concentrations of anti-inflammatory mediators were lower than or equal to the corresponding CSF concentrations in patients without additional injury, whereas

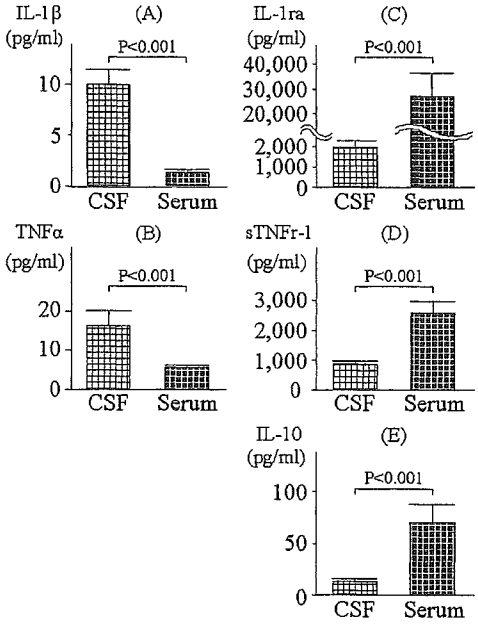

FIG. 2. **Graphs showing CSF and serum concentrations for all substances measured in patients with extracranial additional injury (n = 18).** Open hatched bar, CSF samples. Closed hatched bar, serum samples. Data are expressed as mean ± SEM.

TABLE 2. **CSF mediators in TBI patients based on intracranial pressure (ICP)**

	IL-1β (pg/ml)	TNF-α (pg/ml)	IL-1ra (pg/ml)	sTNFr-I (pg/ml)	IL-10 (pg/ml)
Patients with high ICP* (n = 11)	17.4 ± 2.7	21.8 ± 6.4	2968 ± 597	1351 ± 229	17.4 ± 2.7
Patients with low ICP† (n = 24)	7.2 ± 1.3	15.5 ± 3.1	1263 ± 202	701 ± 69	8.9 ± 1.3
P value	*P* = 0.002	*P* = 0.546	*P* = 0.006	*P* = 0.009	*P* = 0.009

Values are expressed as mean ± SE.
*High ICP: patient's ICP could not be lowered to below 20 mmHg despite conventional treatments.
†Low ICP: patient's ICP was maintained below 20 mmHg by conventional treatments.
P value obtained by Mann-Whitney *U*-test for the difference between the 2 groups.

serum concentrations were markedly higher than the corresponding CSF concentrations in patients with additional injury. Serum concentrations of anti-inflammatory mediators in patients with additional injury were several times higher than those in patients without additional injury. If we put the two patient groups together, concentrations of anti-inflammatory mediators appeared to be higher in serum than in CSF, as was the case for concentrations of IL-10 in our previous study (1). However, it is natural to think that the influence of brain damage on other organ systems is reflected more precisely in the serum samples of patients without additional injury than in those of patients with additional injury. Therefore, we conclude that the excessive increase in serum concentrations of anti-inflammatory mediators after severe TBI is mainly due to additional extracranial injury, not to TBI itself. Our hypothesis is supported by Hensler et al.'s (15) report that plasma levels of IL-10 did not differ between trauma patients with severe TBI and those without severe TBI.

We also observed that serum sTNFr-I concentrations positively correlated with ISS. Our result is in concordance with other published data that sTNFr was correlated with severity of injury (16). Partrick et al. (3) reported that elevated levels of serum sTNFr-I correlated with the development of postinjury multiple organ failure early after trauma (3). There is not much doubt, therefore, that local injury in tissue beds may be likely involved in the increased serum concentrations of sTNFr-I. However, the increased release of sTNFr-I into blood does not seem to be a direct consequence of the secretion of TNF-α

TABLE 3. **CSF mediators in the TBI patients per outcome**

	IL-1β (pg/ml)	TNF-α (pg/ml)	IL-1ra (pg/ml)	sTNFr-I (pg/ml)	IL-10 (pg/ml)
Unfavorable* (n = 14)	14.7 ± 2.5	19.3 ± 5.1	2622 ± 508	1323 ± 190	20.0 ± 5.3
Favorable† (n = 21)	7.5 ± 1.6	16.3 ± 3.6	1249 ± 223	627 ± 49	8.7 ± 1.4
P value	*P* = 0.006	*P* = 0.590	*P* = 0.009	*P* = 0.003	*P* = 0.012

Values are expressed as mean ± SE.
*Patients with a GOS score of 1, 2, or 3.
†Patients with a GOS score of 4 or 5.
P value obtained by Mann-Whitney *U*-test for the difference between the 2 groups.

because serum TNF-α concentration did not differ between patients with and without extracranial additional injury. The mechanisms that induce the release of sTNFr-I into circulation remain to be determined.

What is the function of excessively increased anti-inflammatory mediators in serum after severe TBI? Why are proinflammatory mediators not also increased in serum? These questions cannot be answered with our present data. In 1991, Poutsiaka et al. (17) and Arend et al. (18) reported similarly that TNF-α and IL-1β were not detectable in the circulation of trauma patients despite increased levels of soluble TNF receptor and IL-1ra. Although more than 10 years have passed since they reported their results, the questions just mentioned have yet to be resolved. A key to answering these questions may lie in the answer to another question. Are the excessive anti-inflammatory mediators in serum after severe TBI biologically active? We are now conducting biologic function studies to investigate the biologic activity of these anti-inflammatory mediators in serum in patients with severe TBI.

In our previous study (1), we demonstrated that CSF IL-1β concentration was significantly higher in patients with high ICP than in patients with low ICP ($P < 0.05$) and that CSF IL-1β concentration tended to be higher in patients with an unfavorable outcome than in patients with a favorable outcome ($P = 0.057$). In the present study, we not only confirmed that CSF IL-1β is useful as predictors of outcome in patients with severe TBI, but we also demonstrated that CSF anti-inflammatory mediators were related to high ICP and poor prognosis in patients with severe TBI. Although it is speculated that CSF anti-inflammatory mediators originate from intrathecal synthesis of resident glial cells in the brain or blood leukocytes recruited into the brain (19, 20), the means by which the increased CSF anti-inflammatory mediators act in counteracting the inflammatory response remain unclear. Further study is needed to clarify whether the increase in CSF proinflammatory mediators directly induces the increase in CSF anti-inflammatory mediators or leads indirectly to the increase in CSF anti-inflammatory mediators.

We examined CSF and serum concentrations of anti-inflammatory mediators and proinflammatory mediators in severe TBI patients with and without additional injury. The three primary findings of the present study were as follows: serum concentrations of anti-inflammatory mediators (IL-1ra, sTNFr-I, and IL-10) were much higher than the corresponding CSF concentrations in patients with additional injury, whereas serum concentrations were lower than or equal to the corresponding CSF concentrations in patients without additional injury; CSF concentrations of anti-inflammatory mediators were significantly higher in patients with high ICP than in patients with low ICP; and CSF concentrations of anti-inflammatory mediators were also significantly higher in patients with an unfavorable outcome than in patients with a favorable outcome. On the basis of these findings, we conclude that increased serum concentrations of anti-inflammatory mediators after severe TBI are mainly due to additional extracranial injury and that anti-inflammatory mediators in CSF may be useful indicators of the severity of brain damage in terms of ICP as well as overall prognosis of patients with severe TBI.

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CHANGES IN CSF S100B AND CYTOKINE CONCENTRATIONS IN EARLY-PHASE SEVERE TRAUMATIC BRAIN INJURY

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ABSTRACT—S100B protein (S100B) has been described as a marker of brain injury. Various cytokines also increase in the cerebrospinal fluid (CSF) of patients with severe traumatic brain injury (TBI). Thus, we investigated early changes in the concentrations of CSF S100B and various cytokines after TBI and evaluated the relations of both S100B and cytokines to intracranial pressure (ICP) and prognosis. Twenty-three patients with severe TBI and a Glasgow Coma Scale score of 8 or less on admission were included in this study. CSF and serum samples were obtained on admission and at 6, 12, 24, 48, 72, and 96 h after injury. CSF concentrations of S100B and CSF and serum concentrations of five cytokines (IL-1β, TNF-α, IL-6, IL-8, and IL-10) were measured and compared. The CSF S100B concentration was increased for 6 h after injury and decreased thereafter. The CSF concentrations of IL-6 and IL-8 peaked within 6 h after injury; other cytokines (IL-1β, TNF-α, and IL-10) were elevated for 24 h after injury and gradually decreased thereafter. Peak CSF S100B concentrations correlated significantly with ICP determined at the time CSF samples were taken ($r^2 = 0.729$, $P < 0.0001$). For the cytokines investigated, only the peak CSF IL-1β concentration correlated significantly and positively with the peak CSF S100B concentration ($r^2 = 0.397$, $P < 0.005$). Peak CSF concentrations of S100B (1649 ± 415 μg/L, mean ± SEM) and IL-1β (16.5 ± 3.3 pg/mL) in the 6 patients with high ICP were significantly higher than those (233 ± 67 μg/L, 7.6 ± 1.7 pg/mL, respectively) in the 17 patients with low ICP ($P < 0.05$). The CSF S100B concentration (1231 ± 378 μg/L) in eight patients with an unfavorable outcome was significantly higher than that (267 ± 108 μg/L) in 15 patients with a favorable outcome ($P < 0.05$). The CSF IL-1β concentration (14.8 ± 3.4 pg/mL) in eight patients with an unfavorable outcome tended to be higher than that (7.3 ± 1.5 pg/mL) in 15 patients with a favorable outcome ($P = 0.057$). CSF concentrations of S100B and cytokines peak within 24 h after severe TBI and decrease gradually thereafter. CSF S100B and IL-1β may be useful as predictors of outcome in cases of severe TBI.

KEYWORDS—S100B, cytokine, cerebrospinal fluid, head injury, prognosis

INTRODUCTION

S100B protein is an acidic calcium-binding protein that is present mainly in astroglial cells and Schwann cells (1). S100B is known to modulate glial fibrillary protein and the assembly of intermediate filaments in neuronal or glial cells (2). Elevated serum and cerebrospinal fluid (CSF) S100B concentrations have recently been reported in patients with neurologic disorders and are likely to reflect the degree of brain injury (3–9). Various cytokines are also elevated in the CSF of animals with experimentally induced central nervous system disorders (10, 11) and in humans with central nervous disorders (12, 13). These mediators of immune function are multifunctional and interact with each other, and they may contribute to deleterious secondary brain damage or play a neuroprotective role (14). Recently, increases in CSF S100B and cytokine concentrations have been reported in patients with traumatic brain injury (TBI) (7, 8, 15–19). However, not much is known about changes in CSF S100B and cytokine concentrations during the early posttraumatic phase, especially during the first 24 h after injury. The relation between S100B and cytokines in TBI patients has not been well investigated. We examined changes in CSF S100B and cytokine concentrations in patients with severe TBI during the initial 96-h posttraumatic period and investigated whether the CSF S100B concentration correlates with the CSF cytokine concentrations. Because CSF concentrations of TNF-α, IL-1β, IL-6, IL-8, and IL-10 have been analyzed in severe TBI patients (16–22), we chose to examine these cytokines in the present study. We also assessed the relation of CSF S100B and cytokine concentrations to intracranial pressure (ICP), focal mass volume, and prognosis of such patients with TBI.

MATERIALS AND METHODS

Patient population

Between 1997 and 2001, a total of 53 patients with a Glasgow Coma Scale (GCS) (23) score of 8 or less were admitted to the Department of Traumatology, Osaka University Graduate School of Medicine. Patients less than 10 years of age were excluded from this study. Five patients who suffered severe life-threatening injury to organs other than the brain were also excluded from this study. Serial CSF or serum samples could not be obtained from 25 of the remaining 48 patients; these 25 were, therefore, excluded. Of the 23 patients included in this study, 17 were male, and six were female. Their age averaged 40 years and ranged from 14 to 68 years. No patient had existing prior neurological disease. Informed consent for participating in the study was obtained from an appropriate member of each patient's family.

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Patient management

After intubation, all patients were subjected to continuous mild hyperventilation, which was induced with $Paco_2$ between 30 and 35 mmHg, and all received high-dose barbiturates with mild fluid restriction (1–2 mL/kg/h). On reaching cerebral perfusion pressure (mean arterial blood pressure minus ICP) of less than 60 mmHg, patients were given adequate amounts of albumin. Colloidal fluids or dopamine (3–5 μg/kg/min continuous infusion) was administered as needed to maintain urine output greater than 0.5 mL/kg/h. No corticosteroid or mannitol was administered during the study. Immediately after initial resuscitation, all patients underwent computed tomography (CT) scanning of the head. Subsequently, an intraventricular catheter was placed in each patient. The catheter allowed continuous monitoring of ICP and intracranial temperature. There was no evidence of complications, such as intracranial hemorrhage or infection, as a result of insertion of the intraventricular catheter. Intracranial mass lesions associated with midline displacement greater than 5 mm were surgically removed when necessary. Intracranial hypertension was managed initially in all patients by conventional ICP reduction therapy, such as mild hyperventilation, mild fluid restriction, high-dose barbiturates, and/or CSF drainage. In patients with ICP at or above 20 mmHg and unresponsive to conventional therapy, mild hypothermia (34°C) was induced by surface cooling with a circulating water blanket placed above and below the patient. Intracranial temperature was controlled according to our previously published protocol (24). Control of ICP was achieved in 17 of the 23 patients (low-ICP group) but not in the remaining 6 (high-ICP group). Patients in the low-ICP group were assigned randomly to mild hypothermia (HT, 11 patients) or normothermia (NT, 6 patients). After randomization, HT patients were subjected to mild hypothermia (intracranial temperature = 34°C) as quickly as possible, and NT patients were maintained under normothermic conditions (intracranial temperature = 37°C). Mild hypothermia was started 2.0 ± 0.5 h after injury, and body temperature reached 34°C 6.0 ± 0.5 h after injury. Mild hypothermia was continued for 48 h, and patients were rewarmed at 1°C /day for 3 days. Normothermia (37°C) was maintained for 5 days.

CT study

Focal mass lesions included contusion, subdural hematoma, epidural hematoma, and intracerebral hematoma. Volume measurements of focal mass lesions based on CT images taken during the first 24 h after TBI were obtained according to Cavalieri's Direct Estimator method (25).

CSF and serum analysis

CSF samples were drawn from the intraventricular catheter, and blood samples were drawn from an arterial line immediately after insertion of the intraventricular catheter (initial sampling time was 2.0 ± 0.5 h after injury) and at 6, 12, 24, 48, 72, and 96 h after injury. The CSF samples were centrifuged to remove cellular debris, and the supernatant was immediately frozen at −80°C and stored until analysis. Serum samples were prepared from the blood samples and stored at −80°C until analysis. TNF-α, IL-1β, IL-6, IL-8, and IL-10 concentrations in CSF and serum were analyzed by enzyme-linked immunosorbent assay with commercially available kits (R&D Systems, Minneapolis, MN). The minimum detectable cytokine concentrations were TNF-α 4.4 pg/mL, IL-1β 1 pg/mL, IL-6 0.7 pg/mL, IL-8 10 pg/mL, and IL-10 3.9 pg/mL. For statistical analysis, minimum-detection-level values were used for cytokine concentrations below the minimum detectable levels. CSF S100B concentrations were determined with a commercially available immunoradiometric assay kit (Sangtec Medical, Bromma, Sweden). CSF samples obtained by diagnostic lumbar puncture from seven trauma patients without traumatic brain injury were used as controls.

Patient outcomes

Patient outcome was assessed 6 months after injury on the basis of the Glasgow Outcome Scale (GOS) (26) in which death is scored as 1, vegetative state as 2, severe disability as 3, moderate disability as 4, and good recovery as 5. For statistical comparison, the outcomes of patients with scores of 4 or 5 were considered favorable, and the outcomes of patients with scores of 1, 2, or 3 were considered unfavorable. Surviving patients participated in follow-up interviews either by telephone or in person at the clinic.

Statistical analysis

All values are expressed as mean ± standard error of the mean unless otherwise specified. Statistical analyses were performed with Stat-View computer software (version 5.0) and included Mann-Whitney *U* test, chi-square test, or one-way analysis of variance in combination with the Tukey-Kramer multiple comparisons test. Relations between variables were assessed by Pearson's correlation coefficient. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Patients' characteristics

Of the 23 patients, six made up the "patients with low ICP treated under normothermia" group (NT group), 11 made up the "patients with low ICP treated under mild hypothermia" group (HT group), and six made up the "patients with high ICP" group. All patients with high ICP were treated under mild hypothermia. We had no patients with high ICP treated under normothermia. Clinical characteristics in the three groups are

TABLE 1. **Clinical characteristics of the three study groups**

	Patients with low ICP* treated under normothermia (NT group)	Patients with low ICP* treated under mild hypothermia (HT group)	Patients with high ICP†
No. of patients	6	11	6
Age (yrs)	34 ± 7	37 ± 6	49 ± 8
Sex ratio (M/F)	3/3	11/0	3/3
GCS on admission	5.8 ± 0.8	5.9 ± 0.5	5.0 ± 0.3
CT classification§			
Diffuse injury 1	1	0	0
Diffuse injury 2	3	7	0
Diffuse injury 3	0	0	1
Diffuse injury 4	0	0	0
Evacuated mass lesion	2	4	5
Nonevacuated mass lesion	0	0	0
Additional injuries			
Chest injury	2	1	2
Abdominal injury	0	2	0
Pelvic or leg fracture	0	0	1
Arm fracture	0	0	0
Outcome			
Favorable/unfavorable	6/0	8/3	1/5

Numbers represent number of patients unless otherwise indicated.
Values are expressed as mean ± standard error of the mean.
*Low ICP, patient's ICP was maintained below 20 mmHg by conventional treatments. There were no significant differences between the two groups.
†High ICP, patient's ICP could not be lowered to below 20 mmHg despite conventional treatments. All patients with high ICP were treated under mild hypothermia.
§Categorized according to the classification of Marshall et al. (34).

summarized in Table 1. There were no significant differences between the NT group and the HT group in age, GCS score on admission, focal mass volume, additional injuries, or outcome.

CSF S100B and cytokine concentrations in patients with severe TBI

The mean peak CSF S100B concentration (630 ± 173 μg/L) of the 23 patients with severe TBI was much higher than that (3.3 ± 1.3 μg/L) of the control patients ($P < 0.001$) (Fig. 1). The mean peak CSF cytokine concentrations of the 23 patients were IL-1β 9.9 ± 1.7 pg/mL, TNF-α 23.0 ± 5.7 pg/mL, IL-6 5266 ± 1633 pg/mL, IL-8 12,602 ± 2,115 pg/mL, and IL-10 12.6 ± 2.3 pg/mL. However, the mean CSF cytokine concentrations of the control patients were 1.6 ± 0.2 pg/mL for IL-1β, 11.9 ± 5.0 pg/mL for IL-6, and 96.2 ± 4.3 pg/mL for IL-8. CSF TNF-α and IL-10 concentrations were undetectable in the control patients. All peak CSF cytokine concentrations were significantly higher in the 23 patients with severe TBI than in the control patients ($P < 0.05$) (Fig. 1).

Serial changes in CSF S100B and cytokine concentrations

CSF S100B concentrations increased during the 6-h period immediately after injury and gradually decreased thereafter (Fig. 2A). CSF IL-1β and -α concentrations were substantially higher than those of control patients during the 24-h period immediately after TBI, and they decreased thereafter (Fig. 2, B and C). CSF IL-6 and IL-8 concentrations peaked 6 h after injury and decreased gradually thereafter (Fig. 2, D and E), whereas the CSF IL-10 concentration was substantially higher during the 6-h period immediately after injury but decreased steadily after the initial sampling time (Fig. 2F). During the first 24 h after injury, IL-1β, TNF-α, IL-6, and IL-8 concentrations were two to 100 times higher in CSF than in serum. However, the CSF concentration of IL-10 was lower than the serum concentration.

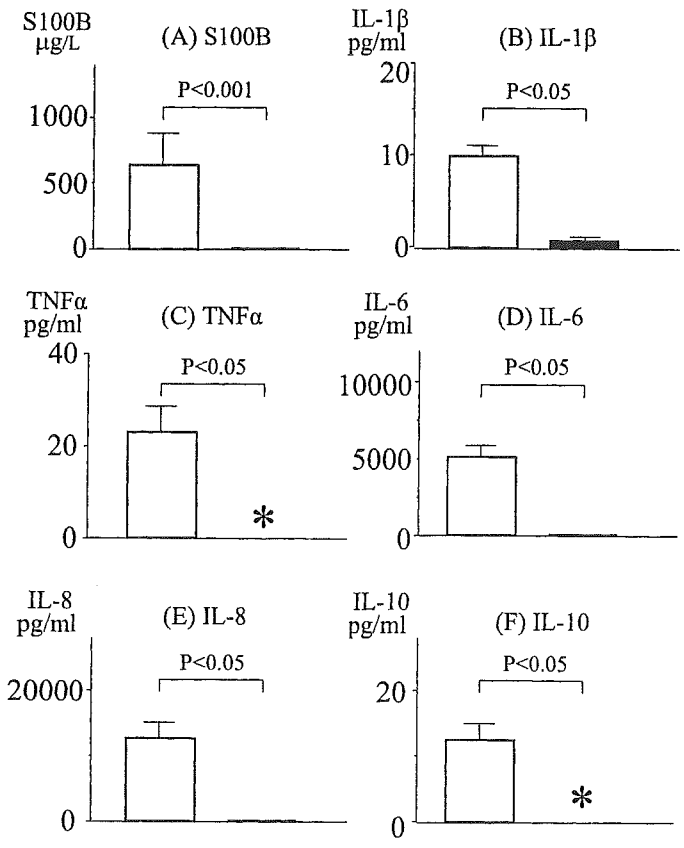

FIG. 1. **Graphs showing peak CSF concentrations of S100B (A) and cytokines (B–F) in 23 patients with severe TBI and controls.** Open bars, patients with severe TBI. Closed bars, control patients. Data are expressed as mean ± SEM values. *CSF TNF-α and IL-10 concentrations were undetectable in the control patients.

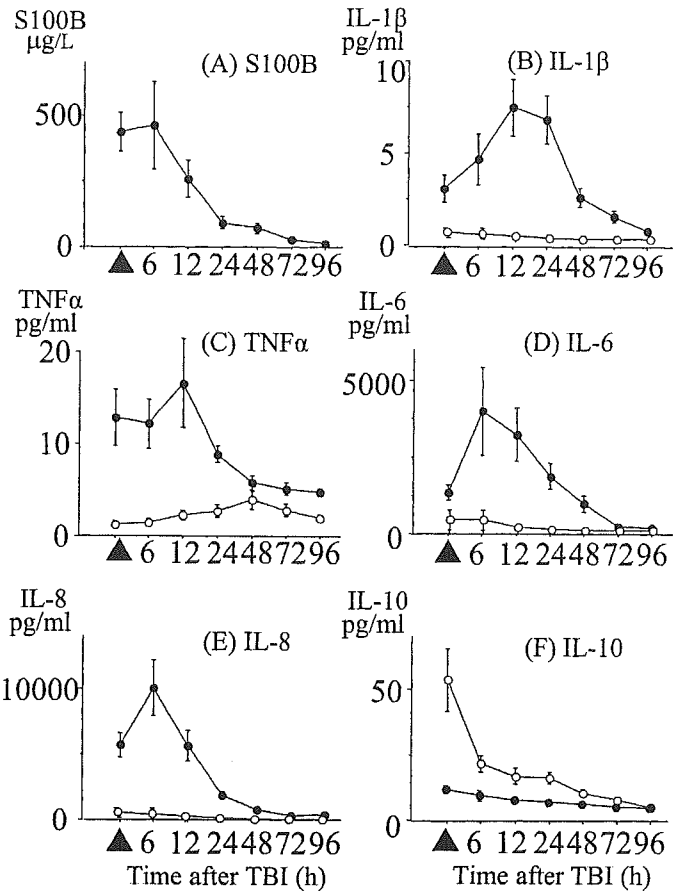

FIG. 2. **Graphs showing serial changes in CSF S100B concentration (A) and serial changes in CSF and serum cytokine concentrations (B–F) in 23 patients with severe TBI.** Data are expressed as mean ± SEM values. ▲, initial sampling time for CSF and serum; ●, CSF S100B and cytokine concentrations; ○, serum cytokine concentrations.

Correlation of ICP with S100B and cytokines

A positive correlation ($r^2 = 0.729$, $P < 0.0001$) was found between peak CSF S100B concentration and ICP at each sampling point (Fig. 3). The CSF S100B concentration was significantly higher in the high-ICP group than in the low-ICP group ($P < 0.001$, Table 2). A significant correlation was found between peak CSF IL-1β concentration and ICP at each sampling point ($r^2 = 0.260$, $P < 0.05$). The CSF IL-1β concentration was also significantly higher in the high-ICP group than in the low-ICP group ($P < 0.05$). No significant correlation was found between other peak CSF cytokine concentrations and ICP at any sampling point.

Serial changes in CSF S100B and cytokine concentrations in HT and NT groups

Serial changes in CSF S100B and cytokine concentrations in the HT group did not differ statistically from changes in the NT

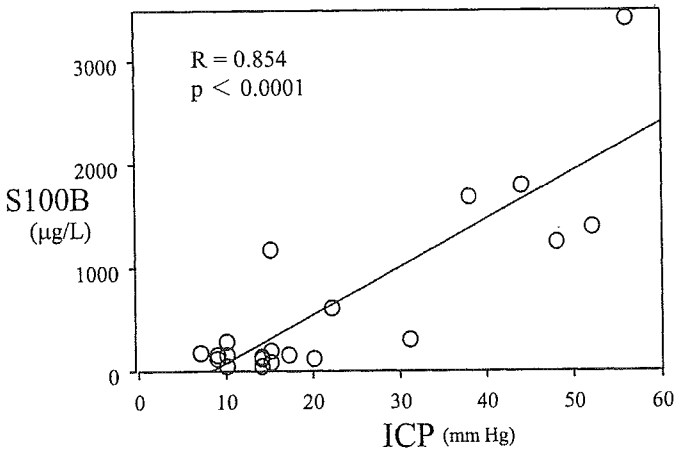

FIG. 3. **Graph showing correlation between ICP and peak CSF S100B concentration in the 23 study patients with severe TBI.** Measurements of ICP and sampling of CSF for S100B assay were done at the same time.

group (Fig. 4). These two groups did not differ significantly in age, GCS score on admission, focal mass volume, level of ICP, additional injuries, or outcome (Table 1).

Correlation of GCS score with S100B and cytokines

No significant correlation was found between the peak CSF S100B concentration and a patient's GCS score on admission. Nor was a significant correlation found between the peak CSF cytokine concentrations and a patient's GCS score on admission.

Correlation of focal mass volume with S100B and cytokines

Significant positive correlation was found between peak CSF S100B concentration and focal mass volume ($r^2 = 0.316$, $P < 0.005$). However, no significant correlations were found between peak CSF cytokine concentrations and focal mass volume.

Correlation between peak CSF S100B and cytokine concentrations

Significant positive correlation ($r^2 = 0.397$, $P < 0.005$) was found between peak CSF S100B concentration and peak CSF IL-1β concentration in the overall study group (Fig. 5). However, no significant correlation was detected between peak CSF concentration of any other cytokine and peak CSF concentration of S100B.

Peak CSF S100B and cytokine concentrations and outcome

At 6 months after TBI, outcome was favorable for 15 patients but unfavorable for eight patients (Table 1). The CSF S100B concentration was significantly higher in patients with an unfavorable outcome than in patients with a favorable outcome ($P < 0.05$) (Table 3). The CSF IL-1β concentration tended to be higher in patients with an unfavorable outcome than in patients with a favorable outcome ($P = 0.057$) (Table 3). No differences were found in CSF concentrations of other cytokines between patients with a favorable outcome and those with an unfavorable outcome (Table 3).

DISCUSSION

In patients with severe TBI, the serum S100B concentration is high on admission, and it decreases gradually (27). However, the changes in CSF S100B that occur early in patients with severe TBI are not clearly understood. The present study showed clearly that the CSF S100B concentration peaked within 6 h after injury and that the peak CSF S100B concentration correlated significantly with ICP determined at the time CSF samples were taken. The mean peak CSF S100B concentration (630 ± 173 μg/L) of the 23 patients with severe TBI was much higher than that (3.3 ± 1.3 μg/L) of the control patients ($P < 0.001$). CSF values from our control subjects were slightly higher than that (1.4 ± 0.2 μg/L) reported by Pleines et al. (7), but we think the actual differences were really very small. Our findings are consistent with those of Hardemark et al. (28), who reported that the CSF S100B concentration peaked 7.5 h after experimental traumatic brain injury in the rat. Hardemark et al. (28) concluded that TBI causes astroglial cells to rupture; thus, the early peak of S100B in CSF may reflect primary brain damage.

Several authors have reported increased serum concentrations of S100B in TBI patients (3–6). Woertgen et al. reported that the serum S100B concentration was significantly higher in patients with an unfavorable outcome than in patients with a favorable outcome (29). Raabe et al. reported a significant correlation between the serum S100B concentration and contusion volume determined from CT scans (30). With respect to TBI, some authors have shown a related increase in S100B in CSF (7, 8, 31). However, details concerning the correlation between CSF S100B concentration and prognosis in patients with severe TBI are not sufficiently understood. In our study, the CSF S100B concentration was significantly higher in patients with an unfavorable outcome than in patients with a favorable outcome. Moreover, the CSF S100B concentration correlated with ICP and with focal mass lesion volume. We believe, therefore, that CSF S100B concentration provides greater prognostic value than serum S100B concentration in the treatment of severe TBI patients.

Early increases in various cytokines in the brain have been reported in rat brain injury models. Reports show that cytokines such as TNF-α, IL-1β, and IL-6 increase, peak within a few hours after brain injury, and then decrease (10, 11). In humans, TBI causes release of various cytokines into the CSF (16, 17, 20, 21). However, in the clinical studies, analysis of cytokine concentrations was performed only on a daily basis, and early changes (within 24 hours) in CSF cytokines in patients with TBI have not been well documented. Like earlier studies in animal models, our study clearly indicated that CSF concentrations of cytokines IL-6 and IL-8 peaked by 6 h after injury, and CSF concentrations of cytokines IL-1β, TNF-α, and IL-10 increased within the first 24 h after injury. Interestingly, CSF concentrations of IL-1β, TNF-α, IL-6, and IL-8 were markedly higher than serum concentrations of these cytokines in our patients. These results are consistent with those of Maier et al. (22), who reported that concentrations of IL-6 and IL-8 were much higher in the CSF than in the plasma of TBI patients. They also found that alterations in the blood–brain

TABLE 2. **Peak concentrations of CSF S100B and CSF cytokines in TBI patients based on intracranial pressure (ICP)**

	S100B (μg/L)	IL-1β (pg/mL)	TNFα (pg/mL)	IL-6 (pg/mL)	IL-8 (pg/mL)	IL-10 (pg/mL)
Patients with high ICP* (n = 6)	1649 ± 415	16.5 ± 3.3	27.1 ± 18.6	5767 ± 1556	6,802 ± 2513	18.1 ± 7.3
Patients with low ICP† (n = 17)	233 ± 67	7.6 ± 1.6	20.8 ± 4.7	5090 ± 2165	14,649 ± 2573	10.7 ± 1.8
P value	$P < 0.001$	$P < 0.05$	$P = 0.195$	$P = 0.207$	$P = 0.092$	$P = 0.483$

Values are expressed as mean ± standard error of the mean.
*High ICP, patient's ICP could not be lowered to below 20 mmHg despite conventional treatments.
†Low ICP, patient's ICP was maintained below 20 mmHg by conventional treatments.
P value obtained by Mann-Whitney *U* test for the difference between the two groups.

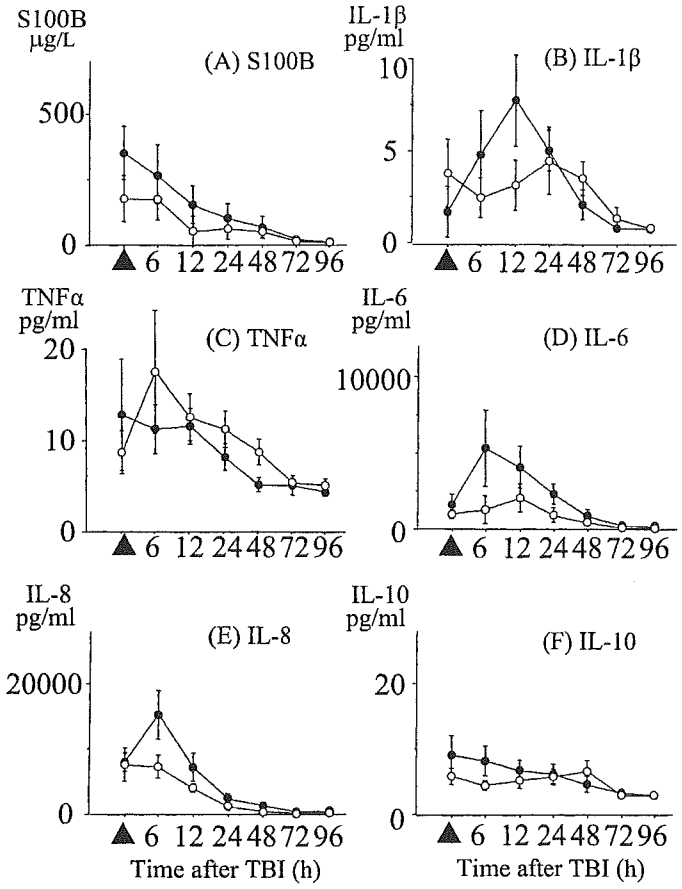

FIG. 4. **Graphs showing serial changes in CSF S100B concentration (A) and serial changes in CSF cytokine concentrations (B–F) in HT group patients (●, n = 11) and NT group patients (○, n = 6).** Data are expressed as mean ± SEM values. ▲, initial sampling time for CSF. There were no significant differences between the two groups.

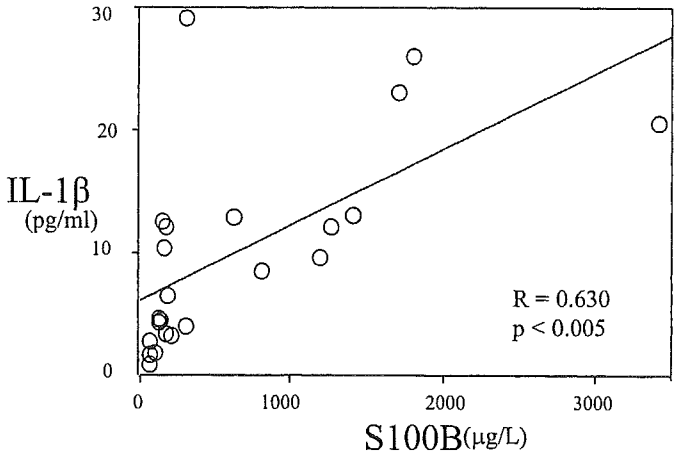

FIG. 5. **Graph showing correlation between peak CSF S100B concentration and peak CSF IL-1β concentration in the 23 study patients with severe TBI.**

barrier seemed not to influence the distribution of cytokines in CSF and plasma after TBI (22). We therefore speculate that these cytokines originate from neurons, microglia, and astrocytes. However, the means by which the excessively increased IL-1β, TNF-α, IL-6, and IL-8 in CSF act in mediating the inflammatory response remain unclear. The relationship between the cerebral inflammatory response and the systemic inflammatory response is yet to be clarified. In contrast to these proinflammatory cytokines, anti-inflammatory IL-10 was concentrated less in CSF than in serum throughout most of the study period. This peculiar distribution of IL-10 was consistent with that reported by Maier et al. (22). We are now investigating the cause of this notable disproportion between inflammatory mediators and anti-inflammatory mediators after TBI.

Barbiturate therapy and mild hypothermia were used in our patients. Barbiturate administration induces human mononuclear leukocytes to release cytokines (32), and S100B may be released by this agent (33). However, whether barbiturate is associated with the increase of S100B and cytokines in the CSF of patients with brain injury could not be determined in this study because all 23 patients received high-dose barbiturates. Although hypothermia has been reported to suppress cytokine production in patients with TBI (22), we found no difference in the serial changes in cytokine concentrations between patients treated under hypothermia and those treated under normothermia.

There are several limitations to our study. First, it may be argued that the number of patients was small and that it is therefore difficult to confirm the relationship between the type of TBI and CSF concentrations of S100B and cytokines. Second, we can not clarify to what degree the increase in CSF S100B and cytokines reflects the extent of ongoing brain damage because it is not ethically feasible to perform CT scanning every 6 h. Third, we can not ascertain serial changes in CSF concentrations of S100B and cytokines because it is difficult to collect CSF samples every 1 or 2 h in the clinical setting. From the present study, therefore, we can not clarify whether the increase in CSF S100B directly induces the increase in CSF IL-1β or leads indirectly to the increase in CSF IL-1β.

We measured CSF concentrations of S100B and cytokines simultaneously during the initial 96 h after severe TBI. The CSF S100B concentration peaked in the early phase of severe TBI, and CSF cytokine concentrations also increased during the early phase or promptly after the CSF S100B elevation.