Cerebrospinal fluid and serum levels of insulin-like growth factor-1 and insulin-like growth factor binding protein-3 in patients with severe head injury

Ağır kafa travmalı hastalarda beyin omurilik sıvısı ve serum IGF-1 ve IGFBP-3 değerleri

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BACKGROUND

The aim of this study is to present time course of insulin like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) levels in both cerebrospinal fluid (CSF) and serum of patients after severe head injury (SHI) and to compare with controls.

METHODS

Our trauma and control groups included 11 consecutive patients with isolated SHI and 9 patients with hydrocephalus (one with normotensive and eight with hydrocephalus due to aqueduct stenosis), respectively. Both serum and cerebrospinal fluid levels of IGF-1 and IGFBP-3 were measured during post-traumatic days and we compared the levels with controls.

RESULTS

Patients and controls showed undetectable levels of both IGF-1 and IGFBP-3 in their CSF. When considering serum levels, patients with SHI had always lower levels of both molecules than that of controls.

CONCLUSION

Administration of IGF-1 during acute, as well as chronic phase of severe head trauma may provide beneficial effects and may decrease both mortality and morbidity in humans with SHI.

Key Words: Brain trauma/drug therapy; IGF-1; IGFBP-3; immunohistochemistry/methods; neuroprotection; severe head injury.

AMAÇ

Bu çalışmanın amacı, insülin benzeri büyüme faktörü-1 (IGF-1) ve insülin-benzeri bağlama protein-3 (IGFBP-3) moleküllerinin ciddi kafa travması sonrası serumda ve beyin omurlik sıvısı'ndaki (BOS) seviyelerini ölçmek ve kontrol grubu ile karşılaştırmaktır.

GEREÇ VE YÖNTEM

Travma ve kontrol gruplarımızı sırası ile ağır kafa travmalı 11 hasta ile 9 hidrosefalili (bir hasta normal basınçlı diğer sekiz hasta akuaduktus stenozuna bağlı hidrosefali) hasta oluşturdu. Hastalardan alınan serum ve BOS örneklerinde IGF-1 ve IGFBP-3 seviyeleri kafa travması sonrası ölçüldü ve seviyeleri kontrol grubu ile karşılaştırıldı.

BULGULAR

Gerek hasta ve gerekse de kontrol grubunda BOS, IGF-1 ve IGFBP-3 seviyeleri ölçülemeyecek derecede düşüktü. Serum seviyelerine bakıldığında ise, hasta grubu kontrol grubuna göre her zaman daha yüksek IGF-1 ve IGFBP-3 değerleri saptandı.

SONUÇ

Ağır kafa travmasının akut veya kronik dönemlerde IGF-1 verilmesi yarar sağlayabilir ve insanlarda mortalite ve morbiditeyi azaltabilir.

Anahtar Sözcükler: Beyin travması/ilaç tedavisi; ciddi kafa yaralanması; IGF-1; IGFBP-3; immünohistokimya/yöntem; nöron korunması.

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The impact of severe head injury (SHI) on the country's economy, emotions of patients' family and most importantly, to the life of the patient is great and it remains still a major public health problem worldwide. Treatment of SHI, up to now, is limited to alleviating the symptoms since secondary mechanisms propagating the neuronal death have not yet been clearly defined. In this context, the study of injury-induced changes of molecules that act to regulate cell death or cell survival, such as neurotropins and other growth factors is essential.

Recent papers indicate that good candidates acting for cell survival are the growth factors and among them insulin-like growth factor-1 (IGF-1) has gained high popularity.[1-4] IGF-1 is a 7.5-kDa peptide that has structural homology to proinsulin and its bioavailability is mainly regulated by six high affinity-binding proteins, namely, insulin-like growth factor binding proteins (IGFBP-1-6) which bind to IGF-1 in the circulation and extracellular matrix.[5,6] It has been demonstrated that IGF-1 was being involved in the neuronal development, thereby it is widely distributed in the central nervous system (CNS) of fetal and neonatal rats, however it is very limited in the adult rat brain.[5]

A precise role for IGF-1 in injured-adult brain remains to be defined, however during the last decade, a number of *in vivo* and *in vitro* studies have shown that IGF-1 was strongly induced in the CNS after different traumatic brain injuries (TBI) such as penetrating injury,[1,3,4] cortical compact injury,[1,7] as well as after spinal cord injury.[8] Moreover, the trophic and reparative properties of IGF-1 treatment following different types of brain injury including trauma have been demonstrated.[1-4]

Proliferative and mitogenic actions of IGF-1 are enhanced or inhibited by IGFBPs depending on the particular IGFBP interacting the cell type and the physiological milieu. Dissociation of IGF-1 from the binding complex allows free IGF-1 to assume biological activity. On the other hand, some recent reports described IGF-independent bioactivity of some IGFBP-3 fragments.[9,10] Thus, we have chosen to measure both cerebrospinal fluid (CSF) and serum levels of IGF-1 and IGFBP-3 because they are thought to provide overall release and activity of IGF-1 which exerts its mitogenic and trophic effects on a variety of cell types in the CNS and regulates astroglial responses after TBI in experimental animals. This study is the first to demonstrate the levels of both IGF-1 and IGFBP-3 in both CSF and serum following SHI in humans.

MATERIALS AND METHODS

Patients and sample collection

Following the admission to our emergency unit, Istanbul University, Cerrahpaşa Medical Faculty, a total of 11 consecutive patients, 6 male, 5 female with a mean age of 27.72±15.27 years with isolated SHI were included in this study. All patients had Glasgow Coma Score (GCS) of ≤8 upon admission and intracranial hematomas were evacuated surgically if necessary. Intraventricular catheters were inserted in all patients immediately after computerized tomographic evaluation and allowed continuous monitoring of the intracranial pressure (ICP) as well as drainage of CSF when the ICP exceeded 20 mmHg. The patients were then treated according to the standardized intensive care protocol and no corticosteroids were used in the treatment. The control group had 6 male and 3 female, with the mean age of 29.22±13.16 years. In the controls, one patient who was 59 year-old, had normotensive hydrocephalus and remaining eight had hydrocephalus due to aqueduct stenosis. Serum samples from the patients and controls were collected from venipuncture while routine blood samples were obtained. CSF samples from the patients were obtained via intraventricular catheter, which is a part of treatment regimen in SHI. CSF from the controls was collected while ventriculo-peritoneal shunting was performed. CSF and serum samples from the controls were obtained once.

On a routine basis, CSF and blood samples were screened for local or systemic bacterial infection and none of the patients showed signs of intrathecal and systemic infections during the study period. The intraventricular catheters were removed when the ICP remained stable at normal values (≤20 mmHg) for at least 24 hours.

Drained intraventricular CSF and paired venous blood samples were collected on days 1, 3, 5, and 10 after trauma. Since seven patients died within the first 10 days of trauma, the number of patients studied in each related day decreased. On days 1 and 3: 11, on day 5: 9, and on day 10: 4 patients were studied. Samples were centrifuged for 10 min at 1500 rpm at 4°C, aliquoted and frozen at -40°C until

analysis and all samples were processed within two months.

CSF and serum obtained from nine patients undergoing ventriculo-peritoneal shunt were used as controls. Since the insertion of the intraventricular catheter for monitoring ICP in patients with GCS of ≤8 on admission after SHI and taking routine venous blood samples are a part of our emergency treatment schedule, the informed consent was not obtained from the next of kin of the patients and this study has been approved by the Local Ethics Committee of Cerrahpaşa Medical Faculty.

The outcome was assessed using the Glasgow Outcome Score (GOS) at 6 months after trauma. Two patients recovered to good outcome (GOS=5), two patients suffered from minor disabilities (GOS=4), and seven patients died (GOS=1) within the first ten days after trauma.

Biochemical assay of IGF-1 and IGFBP-3 in CSF and serum

IGF-1 levels were determined by a solid-phase, enzyme-labeled chemiluminescent immunometric methods in each group on an automatic hormone analyzer (Immulite, DPC, Los Angeles, USA). Reference range for study population was 101-267 ng/mL. Total and within-run CVs of method were 5.8% and 3.5% respectively. Analytical sensitivity of method was 20 ng/mL and specificity was over 99%. The cross reactivity with insulin, LH, TSH and IGF-II were not detected.

IGFBP-3 levels were determined by a solid-phase, enzyme-labeled chemiluminescent immunometric methods in each group on an automatic hormone analyzer (Immulite, DPC, Los Angeles, USA). Reference range for study population was 3.5-7.0 µg/mL total and within-run CVs of method were 8.5% and 4.2% respectively. Analytical sensitivity of method was 0.1 µg/mL and specificity was over 99%. The cross reactivity with IGFBP-I, IGFBP-II and IGF-II were not detected.

Statistical analysis

The software SPSS for Windows 11.0 version was used in the statistical analysis. All values were expressed as mean ± standard deviation unless otherwise specified. For the comparison of age between the patients and control, chi-square test and for the comparison of molecules between the patients and controls for each related day, non-parametric Mann-Whitney U-test was used. Relations between variables were assessed by Pearson's correlation coefficient. Differences were considered statistically significant at $p<0.05$.

RESULTS

We studied 11 patients who suffered from SHI and measured paired CSF and serum concentrations of IGF-1 and IGFBP-3 during 10 days following head trauma. The patient group included 6 male and 5 female, with the mean age of 27.72±15.27 years while control group had 6 male and 3 female, with the mean age of 29.22±13.16 years. We found no statistically significant difference between two groups regarding the age (chi-square; p=0.3). Of the 11 brain-injured patients included in this study, only four survived and recovered to various extends according to the GOS score at 6 months after trauma. Seven died during the study period, thus we were able to collect samples from 11 patients on days 1 and 3, 9 patients on day 5, and 4 patients on day 10 of trauma. Table 1 summarizes the mean CSF and serum concentrations of patients and controls.

IGF-1 levels in CSF and serum

One of the most intriguing finding in this study was that we found undetectable IGF-1 levels in the CSF of both patients and controls in every time points following SHI.

When considering the serum levels of IGF-1, there was a level variation during post-traumatic days, which was mainly due to decrease in the number of patients during the study period. Mean IGF-1 level in the controls was 222.2±185.3 ng/mL, while the mean levels were 104.3±67.9, 88.7±80.2, 219.6±314.6 and 94.9±65.7 ng/mL on days 1, 3, 5 and 10, respectively in the patients. The levels belonging to the patients were always lower than that of controls and we found statistically significant difference between patients and controls on day 1 (p=0.02) and 3 (p=0.01). The highest levels were seen on day 5 although the number of patients was 8 compared to day 1 or 3.

IGFBP-3 levels in CSF and serum

Similar to IGF-1, we found undetectable IGFB-3 levels in the CSF in both patients and controls.

The mean serum level of IGFBP-3 in the controls (42.6±27.2 µg/mL) was significantly higher than

Table 1. Summary of the statistical results of IGF-1 and IGFBP-3 in serum of controls and patients with head injury

Parameters	Patients	Controls (n=9)	P*	MPs (n=5)	MCs (n=6)	P§	FPs (n=6)	FCs (n=3)	P¶	MPs vs FPs (p)	MCs vs FCs (p)
M/F	5/6	6/3									
Mean age (years)	27.7±15.2	29.2±13.1	0.3	25.2±8.8	27.5±7.3	0.6	29.8±19.8	32.6±23.07	0.8	0.28	0.25
IGF-1 (ng/mL)											
• Day 1 (n=11)	104.3±67.9	222.2±185.3	0.02	67.9±43.7	240±224.4	0.17	134.7±72.6	186.6±90.1	0.43	0.14	0.10
• Day 3 (n=11)	88.7±80.2		0.01								
• Day 5 (n=8)	219.6±314.6		0.17								
• Day 10 (n=4)	94.9±65.7		0.14								
IGFBP-3 (µg/mL)											
• Day 1 (n=11)	3.96±2.28	42.6±27.2	0.002	2.78±1.2	34.6±28.2	0.01	4.95±2.5	58.6±19.8	0.02	0.10	0.19
• Day 3 (n=11)	3.57±1.22		0.002								
• Day 5 (n=8)	7.01±8.39		0.005								
• Day 10 (n=4)	2.50±1.19		0.01								

FC: Female controls; FP: Female patients; MC: Male controls; MP: Male patients;
P* compares patients and controls; P§ compares male patients and male controls; P¶ compares female patients and female controls.

patients in all four time points (3.96±2.28, 3.57±1.22, 7.01±8.39 and 2.50±1.19 µg/mL) after trauma. When compared to controls and patients, we found statistically significant difference regarding IGFB-3 levels in serum in all time points (Table 1). It reached to the highest mean level on day 5 parallel to IGF-1.

In general, our study, consistent with those of the literature showed a decreasing trend in the serum levels of both IGF-1 and IGFBP-3 (Fig. 1 and 2). Since we found undetectable IGF-1 and IGFBP-3 levels in the CSF, we could not perform any statistical analysis. Pearson correlation test showed that there was statistically significant correlation between the serum IGF-1 and IGFBP-3 for each corresponding day at the level of p=0.01.

Other factors

Since age and gender were found to have effects on IGF-1 and IGFBPs, we tested whether there was difference between gender in the patients and also in

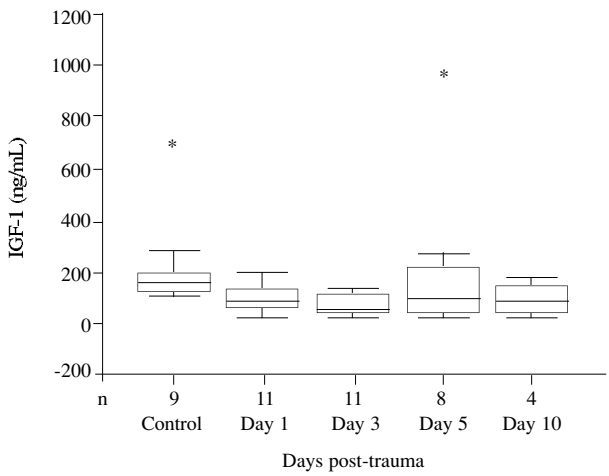

Fig. 1. The levels of IGF-1 in the serum of controls and patients during the post-traumatic days. The peak levels were noted on day 5 post-trauma. *Boxes* denote mean plus the standard error of the mean (SEM) and *vertical lines* denote the range of values. * indicates extreme values.

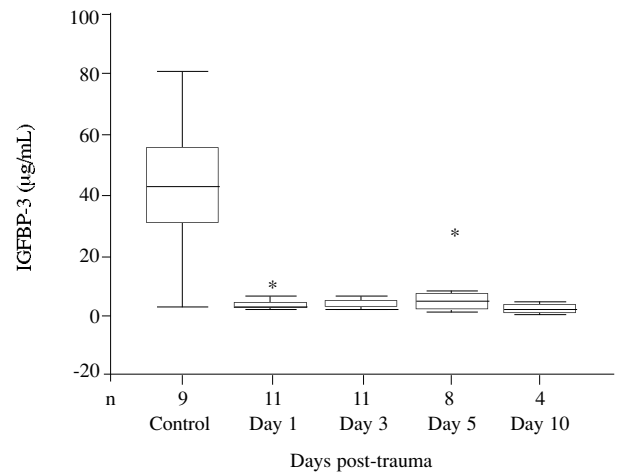

Fig. 2. Time course of IGFBP-3 in the serum of patients after severe head injury and in serum of controls. The peak value was noted on day 5, coincident with IGF-1. *Boxes* denote mean plus the standard error of the mean (SEM) and *vertical lines* denote the range of values. * indicates extreme values.

the controls. We compared the serum IGF-1 and IGFBP-3 levels measured on day 1 only because in the early post-traumatic time, the patients had not yet received dopamine, which has been thought to influence circulating IGF-1 levels. The mean age of male and female patients were 25.2±8.8 and 29.8±19.8 years, respectively and no statistically significant difference was found (p=0.28). The mean serum levels of IGF-1 in male and female patients were 67.9±43.7 and 134.7±72.6 ng/mL, respectively. We found no statistically significant difference between male and female patients regarding IGF-1 serum levels (p=0.14). Female patients also had higher IGFBP-3 serum levels than male patients as in IGF-1. The mean IGFBP-3 level in serum of males was 2.78±1.2, whilst it was 4.95±2.5 µg/mL in females in patient group. There was statistically significant difference between male and female of patients regarding serum IGFBP-3 levels (p=0.10). We also compared male and females in the control group regarding age, IGF-1 and IGFBP-3 levels. The mean age were 27.5±7.3 and 32.6±23.07 years, respectively and no difference was found (p=0.25). Males had higher mean levels of IGF-1 on day 1 post-trauma than females in the controls (240±224.4 vs 186.6±90.1 ng/mL), however the number of females was 3, while it was 6 in males. No significant difference was found between males and females in the controls regarding IGF-1 serum levels (p=0.10). When considering serum IGFBP-3 levels in males and females in controls, females had higher mean level than males on day 1 post-trauma (58.6±19.8 vs 34.6±28.2 µg/mL) even though the number of females were half of males in controls. We found no statistically significant difference (p=0.19).

We also compared the levels in males and in females between patients and controls. Males and females in controls had higher serum levels of both IGF-1 and IGFBP-3 than males and females in patients when compared with day 1 post-trauma. Difference between mean age in either females or males did not reach statistically significant difference within the patient and control groups (Table 1). Mean serum levels of IGF-1 in males between patients and controls were 67.9±43.7 and 240±224.4 ng/mL, respectively and no statistically significant difference was found (p=0.17). There was also no statistically significant difference between IGF-1 serum levels regarding females in patients and controls (134.7±72.6 vs 186.6±90.1; p=0.43). However; IGFBP-3 serum levels showed significantly difference in males between patients and controls and in females between patients and controls. The mean serum levels of IGFBP-3 were 2.78±1.2 and 34.6±28.2 µg/mL in male patients and male controls, respectively. The difference demonstrated statistically significance (p=0.01). Similarly, the mean levels were 4.95±2.5 and 58.6±19.8 µg/mL in female patients and female controls, respectively. The difference was found to be statistically different (p=0.02), suggesting that SHI caused significant decrease in IGF-1 and IGF-3 irrespective of age and gender.

DISCUSSION

In this study, the time courses of IGF-1 and IGFBP-3 both in the CSF and serum of patients after SHI were demonstrated for the first time. IGF-1 and IGFBP-3 levels in the CSF were so low that the levels were marked as "undetected" in both groups but the circulating levels of both molecules were significantly decreased in patients with SHI when compared with controls, consisting with the previously published experimental and clinical studies.[1,3,4,11] Moreover, in the current study, females in both patients and controls demonstrated higher serum levels of molecules tested than males that support the results of some studies[12] but in contrast with others.[11] It has been demonstrated that dopamine in critically ill patients decreased the circulating level of IGF-1,[13,14] thus we compared the levels of IGF-1 and IGFBP-3 before the patients received dopamine in our intensive care unit (on day 1). The results showed significant decrease in circulating levels of both molecules, suggesting that it is unlikely to be a result of the infusion of dopamine during the study period. We also showed that age and gender had no effect on the circulating levels of IGF-1 and IGFBP-3 in patients with SHI but the authors underlined that this discrepancy between the majorities of experimental and/or a few clinical study and our results may largely be due to the small number of the patients included in our study.

Alterations of pituitary functions after head injury has been demonstrated and these alterations become apparent during the first hours or days after head trauma and persist for the duration of acute phase of the illness.[15-17] However, this pituitary function

derangements, especially GH/IGF-1 axis, recovered to their normal circulating levels at least 1 month following head trauma,[15] thereby administration of IGF-1 may be beneficial during the early periods of SHI since head-injured patients are known to suffer from hypermetabolism, hypercatabolism and hyperglycemia, suggesting the ability of IGF-1 administration to decrease blood glucose and increase body weight.

The reparative and neuroprotective properties of IGF-1 administration have been demonstrated in various in vitro and in vivo studies, respectively. In cell cultures, IGF-1 enhances neuronal survival and differentiation and neurite outgrowth is promoted.[18-20] By preventing loss of intercellular calcium homeostasis and mitochondrial transmembrane potential, IGF-1 prevents neurons against hypoxic and calcium-mediated hypoglycemic damage.[21,22] Axonal regeneration is stimulated by local administration of IGF-1 in peripheral nerve injuries.[23,24] It has been also demonstrated that intracerebroventricular IGF-1 administration in transient forebrain ischemia and experimental hypoxic ischemia markedly reduced neuronal loss in injured areas.[25,26]

It seems that the neurons and the astrocytes are the main sources of IGF-1 whilst, the choroids plexus is a likely source of IGFBP-3 demonstrated in rats exposed to penetrating brain injury.[1] Walter, et al.[1] showed expression of IGF-1 mRNA and IGFBP-3 mRNA peaked on day 7 following penetrating injury and prominent levels of IGFBP-3 was associated with blood vessels, suggesting a role of IGFBP-3 in modulating IGF-1 efflux into the brain from the circulation. The authors measured little or no IGF-1 in the CSF but high levels in the serum after penetrating brain injury in rats, suggesting CNS wounds are the focus of an angiogenic response. According to the authors, the presence of IGFBP-3 in capillary endothelial cells explains the possible route of entry of IGF-1 from the blood into the lesion. The results are somewhat similar to our results since we also detected little or no IGF-1 and/or IGFBP-3 in the CSF. Transport of IGF-1/IGFBP-3 complex through the ventricles and the subarachnoid space to the sites of sequestration and activity in brain parenchyma explains why there is little or no IGF-1 or IGFBP-3 in the CSF. Following the lateral fluid percussion injury in rats, both periodic and continuous systemic administration of IGF-1 improved neurological motor and cognitive outcome.[2]

Neuroprotective effects of IGF-1 after a penetrating brain injury have also been stated in recent two papers by Kazanis, et al.[3,4] who demonstrated administration of IGF-1 has beneficial effects on the general health condition of the animals and counteracted the injury-induced body weight loss. Furthermore, IGF-1 increased the survival rate of the injured animals. IGF-1 decreased the number of Hsp70 protein, a marker of neuronal death, and TUNEL positive cells. Studies suggested that neuroprotective effects of IFG-1 are manifested not only at the cellular level but also on the general health conditions of the injured animals. Thereby, besides the neuroprotective features at the cellular level, anabolic role of IGF-1 at the systemic level may also be important for the patients with SHI since long-term protection to mature oligodendrocytes, mainly by inhibiting apoptosis, is vital.[27,28]

CONCLUSION

We demonstrated for the first time that IGF-1 and IGFBP-3 levels are significantly decreased in the blood and are undetectable in the CSF. Administration of IGF-1 during acute as well as chronic phase of head trauma may provide beneficial effects and may decrease mortality and morbidity rates after SHI.

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