

Alteration in brain natriuretic peptide (BNP) plasma concentration following severe traumatic brain injury

G. E. Sviri, J. F. Soustiel, and M. Zaaroor

Department of Neurosurgery, Rambam (Maimonides) Medical Center, Technion-Israel Institute of Technology, Haifa, Israel

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Summary

Background. Brain natriuretic peptide (BNP) is a potent natriuretic and vasodilator factor which, by its systemic effects, can decrease cerebral blood flow (CBF). In aneurysmal subarachnoid hemorrhage (aSAH), BNP plasma concentrations were found to be associated with hyponatremia and were progressively elevated in patients who eventually developed delayed ischemic deficit secondary to vasospasm. The purpose of the present study was to evaluate trends in BNP plasma concentrations during the acute phase following severe (traumatic brain injury) TBI.

Methods. BNP plasma concentration was evaluated in 30 patients with severe isolated head injury (GCS < 8 on admission) in four time periods after the injury (period 1: days 1–2; period 2: days 4–5; period 3: days 7–8; period 4: days 10–11). All patients were monitored for ICP during the first week after the injury.

Findings. The initial BNP plasma concentrations (42 ± 36.9 pg/ml) were 7.3 fold ($p < 0.01$) higher in TBI patients as compared to the control group (5.78 ± 1.90 pg/ml). BNP plasma concentrations were progressively elevated through days 7–8 after the injury in patients with diffused SAH as compared to patients with mild or no SAH ($p < 0.001$) and in patients with elevated ICP as compared to patients without elevated ICP ($p < 0.001$). Furthermore, trends in BNP plasma concentrations were significantly and positively associated with poor outcome.

Interpretation. BNP plasma concentrations are elevated shortly after head injury and are continuously elevated during the acute phase in patients with more extensive SAH and in those with elevated ICP, and correlate with poor outcomes. Further studies should be undertaken to evaluate the role of BNP in TBI pathophysiology.

Keywords: Brain natriuretic peptide; head injury; intracranial hypertension; subarachnoid hemorrhage.

Introduction

Brain natriuretic peptide (BNP) is a potent natriuretic and diuretic factor with very effective vasodilator activity [8]. It is mainly produced and released by the cardiac

ventricle in response to overload, and to sympathetic and humeral stimulus [7, 12]. By its systemic effect, BNP reduces blood pressure (BP) and plasma volume [8]. In aneurysmal subarachnoid hemorrhage (SAH), BNP plasma concentrations were found to be elevated and responsible for the profound diuresis and natriuresis observed in many patients [1, 19]. Due to its effect on BP and plasma volume, it has been suggested that elevated plasma BNP concentration might exacerbate cerebral blood flow (CBF) reduction in cerebral vasospasm [1, 10, 16, 17, 19].

The role of natriuretic peptides (NPs) in acute traumatic brain injury has not been studied, and there are few reports of hyponatremia following TBI associated with elevated plasma concentrations of atrial natriuretic peptide (ANP) [2, 13, 14, 23]. The purpose of the present study was to evaluate trends in BNP plasma concentrations in patients with isolated severe TBI during the first 12 days after injury in relation to the type of injury, extent of SAH hemorrhage, intracranial pressure (ICP) and neurological outcome.

Patients and methods

Patients

The study population included 30 patients with severe isolated TBI (Glasgow coma score 8 or less on admission [18]). Patients with ischemic heart disease, congestive heart failure, hypertension and/or chronic renal failure were excluded, to rule out the possibility of bias due to cardiovascular or systemic disease. Patients who died within the first week after the injury were also excluded from the study.

Table 1. *Clinical and demographic data*

	No. of patients
Age	
31.4 ± 14 years	
Male/female	24/6
Type of injury	
diffuse axonal injury	21
subdural hematoma	9
epidural hematoma	3
brain contusions	9
Subarachnoid hemorrhage-intensity	
Fisher's scores 1 + 2	17
Fisher's scores 3 + 4	13
Intracranial pressure	
controlled	18
elevated controlled	7
refractory elevated	5
Glasgow outcome score	
favorable (4–5)	11
unfavorable (1–3)	19

There were 24 male and 6 female patients, ranging in age from 16 to 69 years, with a mean of 32.4 years (SD ± 14 years) (clinical and demographic data are presented in Table 1). The clinical data were collected prospectively. Final neurological outcome was assessed by the Glasgow Outcome Scale (GOS) score [6] for all patients six months after the injury. Patients were divided into two clinical subsets: those without intracranial hypertension (ICH) (ICP < 20 mm Hg) under treatment with sedative drug and head elevation and those with increased ICP (ICP > 20 mm Hg) under the same treatment. The last group was further divided into two sub-groups: patients with controlled intracranial hypertension (ICP < 25 mm Hg) under further treatment with mild hyperventilation (PCO₂ 30–35 mm Hg) and Mannitol, and those with intractable elevated ICP (ICP > 25 mm Hg) in spite of this treatment.

Management protocol

All patients were seen in the Emergency Room and received primary care as recommended by ATLS specifications. Surgical masses were evacuated by craniotomy as indicated (for patient with ICH and/or midline shift > 5 mm). All patients were admitted to the Neurosurgical Intensive Care Unit and were continually monitored for intracranial pressure using a subdural located tube catheter in the right frontal region. ICP was monitored for a minimum of 7 days. The treatment protocol included sedation with continuous propofol administration (3–5 mg/kg/h), analgesia with fentanyl, and head elevation. Patients with elevated ICP were further treated by mild hyperventilation (target PCO₂ values between 30–35 mm Hg) with Mannitol 20% (0.5–1 gr/kg/4h). Patients with refractory elevated ICP (>25 mm Hg) under this treatment were further treated with Penthotal (3 mg/kg/h) or ventriculostomy.

CT findings

Lesions present on initial CT scan were categorized according to Marshall's scoring system [9] (Table 1). CT findings were consistent with diffuse axonal injury (DAI) in 21 patients expressed by either diffuse subarachnoid hemorrhage in 12 cases or punctiform intraparenchymal hemorrhages in six cases. Acute epidural hematomas were found in three patients, acute subdural hematomas in nine, and cerebral

contusion in nine. Nine patients harbored a single post-traumatic finding on initial CT scan while multiple lesions or diffuse injury were found in the remaining patients. Extent of SAH was scored according to Fisher's classification [3] for spontaneous SAH, based on the initial CT finding (Fisher's scores 1 + 2 and Fisher's scores 3 + 4).

Blood tests

Phlebotomy was performed for plasma sampling of BNP concentration, which was measured four times during the first 11 days after the injury at fixed intervals, defining four periods within the clinical course: Period 1 – between days 1–2 (day 1 being regarded as the day of injury); Period 2 – between days 4–5; Period 3 – between days 7–8, Period 4 – between days 10–11. Blood samples were collected in chilled syringes and transferred into polypropylene tubes containing 7.5 mg potassium ethylenediamine tetraacetic acid (EDTA) and aprotinin (1000 kIU/ml) at 4 °C, and centrifuged at 4000 RPM for 15 min at 4 °C. Plasma was stored at –70 °C and assayed within six months. Plasma BNP levels were determined using a specific immunoradiometric assay (SHIONORIA BNP, Shionogi & Co Ltd), based on methods previously reported [16, 19]. Blood samples were also collected from 10 healthy volunteers to determine normal BNP plasma concentrations.

Statistical analysis

For statistical purposes, trends in BNP plasma concentrations were analyzed by means and standard error of the mean. BNP-concentration groups were compared by means of non-parametric ANOVA and Student's T test. Differences were considered to be significant when they reached a *p* value of less than 0.05.

Results

Clinical features and results are summarized in Table 1. BNP plasma concentrations were found to be significantly higher in the patient group (Period 1: 42 ± 36.9 pg/ml; Period 2: 47.6 ± 70.1 pg/ml; Period 3: 52.3 ± 147.6 pg/ml; Period 4: 46.77 ± 58 pg/ml) than in the control group (5.78 ± 1.90 pg/ml, *p* < 0.01), although the concentrations were scattered over a wide range of values (min: 0/9 pg/ml; max: 668.9 pg/ml).

BNP and extent of SAH

BNP plasma concentrations were found to be significantly elevated (Table 1; Fig. 1) in patients (n-17) with Fisher's 1–2 SAH in Period 1 as compared to Period 3–4 (30.5 ± 22.2 pg/ml vs 9.6 ± 8 pg/ml and 7.1 ± 5.4 pg/ml, respectively, *p* < 0.001) as well as in Period 2 as compared to Period 4 (28.3 ± 41.9 pg/ml vs 7.1 ± 5.4 pg/ml, *p* < 0.01). In patients (n-13) with diffuse SAH, BNP plasma concentrations were elevated but did not change significantly during the course of the study (Fig. 1). Although there were no significant differences in the BNP plasma concentrations in the first period between patients with mild 1–2 (n-17) and diffuse

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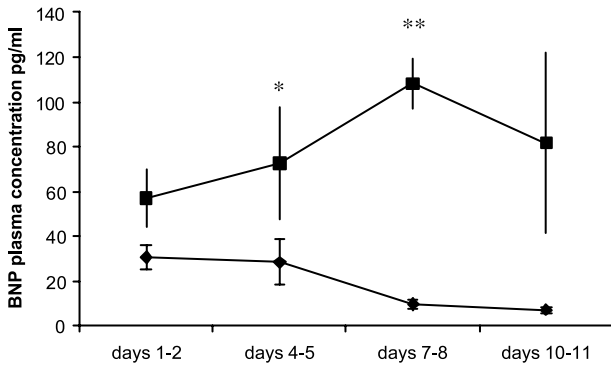


Fig. 1. Graph showing the BNP plasma concentration (mean) on days 1-2; 4-5; 7-8; 10-11 (day 1 regarded as day of injury) and traumatic SAH intensity. Plasma BNP concentrations are significantly more elevated on days 4-5 and 7-8 in patients with initial traumatic SAH classified as Fisher's score 3+4 compared to patients with initial traumatic SAH classified as Fisher's score 1+2. Significance: * $p < 0.01$, ** $p < 0.001$, the perpendicular lines represent standard error of mean. —◆— Fisher 1 & 2; —■— Fisher 3 & 4

SAH (n-13) (30.54 ± 54.9 pg/ml vs 57.1 ± 46.9 pg/ml, Fig. 1). The BNP concentration in Periods 2 and 3 were significantly higher in patients with diffuse SAH as compared to patients with mild SAH (72.6 ± 91.2 pg/ml vs 28.3 ± 41.9 pg/ml and 108.2 ± 40.3 pg/ml vs 9.6 ± 8.9 pg/ml for Periods 2 and 3, respectively, $p < 0.001$; Table 1, Fig. 1).

BNP and intracranial pressure

In patients (n-18) without elevated ICP, BNP plasma concentrations decreased progressively between the first

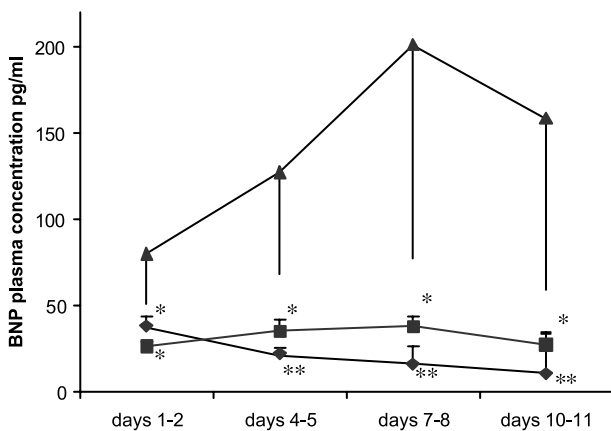


Fig. 2. Graph showing the BNP plasma concentration (mean) on days 1-2; 4-5; 7-8; 10-11 (day 1 regarded as day of injury) and intracranial pressure. Plasma BNP concentrations are significantly more elevated in all time periods in patients with refractory intracranial hypertension (ICH) compared with the values of patients without ICH and controlled ICH. Significance: * $p < 0.05$, ** $p < 0.01$, the perpendicular lines represent standard error of mean. —◆— No ICH; —■— Controlled ICH; —▲— Refractory ICH

and fourth periods (Period 1: 37.6 ± 26.9 pg/ml; Period 2: 21.5 ± 17.3 pg/ml; Period 3: 16.7 ± 42.9 pg/ml, $p < 0.001$, Period 4: 10.9 ± 22.9 pg/ml $p < 0.001$, Fig. 2), while in patients (n-7) with elevated controlled ICP the BNP plasma concentrations were found to be continuously elevated throughout the study periods (Period 1: 26.4 ± 9.6 pg/ml; Period 2: 35.3 ± 17.5 pg/ml; Period 3: 37.9 ± 20.9 pg/ml, Period 4: 27.4 ± 19.7 pg/ml, Fig. 2). Furthermore, in patients (n-5) with refractory elevated ICP, BNP plasma concentrations were found to be progressively elevated between the first and third periods (Period 1: 79.97 ± 65.8 pg/ml; Period 2: 127.2 ± 131.4 pg/ml; Period 3: 200.8 ± 275.6 pg/ml; Period 4: 157.3 ± 222 pg/ml, Fig. 3). In these patients, BNP levels were significantly more elevated in all the studied periods as compared to patients with no ICP or elevated controlled ICP ($p < 0.05$).

BNP plasma concentrations and outcome

Patients (n-19) with an unfavorable outcome (GOS 1-3) had significantly higher BNP plasma ratio concentrations in Period 3 as compared to Period 1 (Period 3/1) and Period 4 compared to Period 1 (Period 4/1) in compared to patients (n-11) with favorable outcomes (COS 4-5) (Period 3/1: 1.51 ± 0.74 vs 0.52 ± 0.031 , $p < 0.01$; Period 4/1: 1.09 vs 0.31 ± 0.026 , $p < 0.01$). Two patients died during the study period at the beginning of the second week and the last blood samplings in these patients revealed extremely high BNP concentrations (668.9 pg/ml and 267 pg/ml).

Discussion

The results of the present study suggest that BNP plasma concentrations are elevated shortly after head injury; in patients with diffuse SAH, these values were continually and progressively elevated between days 1 and 8 following the course as patients with aneurysmal SAH [10, 16, 17, 19]. These findings raise major questions concerning the role of BNP in head injury. BNP is mainly produced and secreted from the heart ventricle in response to overload and was found to be elevated in patients with congestive heart failure [5, 21]. In aSAH, Tomida *et al.* [19] and Wijdicks *et al.* [22] have suggested that increased BNP plasma concentrations can be of cardiac origin. According to Tomida *et al.* [19], augmented cardiac release of BNP may be triggered by stress and noradrenaline release. Wijdicks *et al.* [22] suggested that the initial bleeding in SAH might result

in hypothalamic injury, especially in the rupture of an anterior circulation aneurysm. They assumed that such a hypothalamic insult might, in turn, cause cardiac lesions with subsequent BNP secretion. This cardiac stress may be secondary to an increase in sympathetic flow. Tsubokawa *et al.* [2] reported that patients with high grade SAH due to rupture of an anterior communicating artery aneurysm showed a significantly higher concentration of BNP compared to lower grade patients, and suggested that hypersecretion of BNP is caused by direct mechanical damage to the anterior hypothalamus by a ruptured Acom aneurysm. The high circulatory levels of BNP, which were found after TBI, might suggest that the initial injury induced markedly increased production of BNP from the heart ventricles as a result of increased sympathetic flow, the same mechanism as suggested for aneurysmal SAH. According to Tsubokawa *et al.* [20] a higher increase of BNP is observed in patients suffering from severe neurological deficit findings, which are similar to our findings showing significant correlation between trends in BNP plasma concentration and outcome.

In the present study, BNP concentrations remained elevated or continuously increased in patients with elevated ICP. Fukui *et al.* [4] reported that mean serum ANP and BNP levels in patients with focal brain edema were significantly higher than those in patients without focal brain edema between days 4 and 14, and suggested that focal brain edema may have some role in the pathogenesis of excessive secretions of ANP and BNP during the sub-acute phase of SAH. NPs have a regulatory role in brain water and electrolyte content and were found in different experimental animal model to reduce ICP and brain edema [11, 15]. At present, it is unclear whether this elevation in heart response to volume overload fluid and mannitol administration increased sympathetic outflow or reflects a compensatory counter-mechanism aimed at reduction of brain edema. In any event, since BNP can reduce systemic BP and decrease plasma volumes, it can exacerbate cerebral blood flow reduction in patients with increased ICP. Furthermore, the continual elevation of BNP in the plasma was significantly associated with a poor long-term outcome. This may reflect an increase in the sympathetic flow of patients with more significant injury resulting in increased production of BNP from the ventricles. Although the mechanism for the release of BNP and its role in the pathophysiology of TBI is unclear, the findings in the present study suggest that, as in aneurysmal SAH, elevated BNP concentrations are associated with more sig-

nificant primary and secondary brain insults and poor outcome [16, 17, 19, 20].

Conclusion

BNP plasma concentration is elevated shortly after head injury and is continuously elevated in patients with elevated ICP, diffuse SAH, and patients with poor outcome. Whether this elevation results from the heart's response to fluid and Mannitol administration, increased sympathetic outflow, or reflects a compensatory counter-mechanism aimed toward reduction of brain edema is not clear and should be further evaluated.

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Correspondence: Gill E. Sviri, Department of Neurological Surgery, Rambam (Maimonides) Medical Center, P.O.B.-9602, Haifa 31096, Israel.