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Clinical and prognostic value of IL-6 and IL-2 monitoring in patients with severe traumatic brain injury

© A.A. Sychev[1], I.A. Savin[1], G.V. Danilov[1], A.I. Baranich[1], K.O. Kakurin[2], Yu.V. Strunina[1], A.V. Oshorov[1], A.D. Kravchuk[1]

[1]Burdenko Neurosurgery Center, Moscow, Russia;
[2]Pirogov Russian National Research Medical University, Moscow, Russia.

ABSTRACT

Traumatic brain injury (TBI) is characterized by high mortality and severe disability worldwide representing a major social, economic, and medical problem. Pathogenesis of secondary brain damage is underpinned by a cascade of neuroinflammatory reactions triggered by cytokine release. Key mediators include interleukin-6 (IL-6) and interleukin-2 (sIL-2R) system. However, their daily dynamics in acute period of severe trauma and relationship with intracranial hypertension remain poorly understood.

Material and methods. The study was conducted at the Burdenko Neurosurgical Center. Inclusion criteria: acute TBI, admission within 24 hours, age 18—75 years. Exclusion criteria: atonic coma, decompensation of chronic diseases. IL-6, sIL-2R, C-reactive protein, and procalcitonin were assessed.

Results. There were 74 patients with severe TBI (19 women, mean age 34.0±12.5 years). The mortality rate was 14.9% (11 patients). Biphasic cytokine dynamics was revealed. Early increase in IL-6 on day 1 reflected extent of primary injury. On the 2nd day, IL-6 levels remained significantly higher in patients with fatal outcome (median 40.2 vs. 22.4 pg/ml, $p<0.05$). Secondary increase was recorded after 3 days and coincided with manifestation of infectious complications peaking on day 5. On day 5, sIL-2R levels were found to be more than 2.5-fold higher in patients with fatal outcome (1660.0 vs. 649.0 pg/ml, $p<0.05$). In fatal patients, we found strong direct correlation between IL-6 and intracranial pressure (rho=0.71), as well as inverse correlation with cerebral perfusion pressure.

Conclusion. Biphasic cytokine response develops in acute phase of severe traumatic brain injury. Early phase (2 days) is characterized by increased IL-6 according to extent of primary cerebral injury. The second phase (days 3—14) is associated with infectious complications and characterized by increased sIL-2R and IL-6. It is not their absolute value, but temporal dynamics is prognostically significant. No IL-6 reduction by 48 hours after injury indicates uncontrollable neuroinflammation and potentially unfavorable outcomes. Peak (more than 2.5 times) increase in sIL-2R on day 5 is a marker of transformation of protective inflammation into systemic hyperinflammatory syndrome. Direct correlation between IL-6 and intracranial hypertension in fatal patients confirms pathogenetic role of this cytokine in secondary brain injury. IL-6 and sIL-2R monitoring may enable timely identification of patients with high risk of fatal intracranial hypertension and ensure a personalized approach to intensive care.

Keywords: *TBI, neuroinflammation, cytokines, interleukin, infection, trauma.*

INFORMATION ABOUT THE AUTHORS:
Sychev A.A. — https://orcid.org/0000-0002-0038-1005
Savin A.V. — https://orcid.org/0000-0003-3874-4147
Danilov G.V. — https://orcid.org/0000-0003-1442-5993
Baranich A.I. — https://orcid.org/0000-0002-1167-0742
Kakurin K.O. — https://orcid.org/0009-0003-6439-8070
Strunina Yu.V. — https://orcid.org/0000-0001-5010-6661
Oshorov A.V. — https://orcid.org/0000-0002-3674-252x
Kravchuk A.D. — https://orcid.org/0000-0002-3112-8256
Corresponding author: Baranich A.I. — e-mail: anastasia.baranich@gmail.com

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Introduction

Traumatic brain injury (TBI) is characterized by high mortality and severe disability worldwide, representing a major social, economic and medical problem [1]. Pathogenesis of secondary brain damage is based on a cascade of neuroinflammatory reactions triggered by cytokine release in response to primary traumatic injury, hemorrhage and ischemia [2—4]. A key component of this cascade is blood–brain barrier disruption following activation of matrix metalloproteinase-9. This enzyme disrupts intercellular contacts with attraction of neutrophils, leu-

kocytes and monocytes into the injury site with progression of brain edema [5—8].

The key mediators initiating and maintaining these processes are interleukin-6 (IL-6) and soluble interleukin-2 receptor (sIL-2R). Among inflammatory mediators, IL-6 released by activated microglia and astrocytes is the most important [9, 10]. Despite experimental data on its neuroprotective potential, clinical studies associate persistent increases in IL-6 with adverse outcomes [11, 12]. Another key regulator is interleukin-2 (IL-2), whose activity is assessed by its soluble receptor (sIL-2R) [13]. IL-2 is involved in neuroimmune interactions with complex effect on blood-brain barrier permeability and processes of neuroregeneration [9, 14—15].

Despite the recognized role of these cytokines in pathogenesis of TBI, the detailed diurnal dynamics of IL-6 and sIL-2R in acute period of severe trauma, as well as their relationship with intracranial hypertension is still unclear.

The purpose of this study was to investigate diurnal dynamics of IL-6 and sIL-2R in acute phase of severe TBI and to assess their prognostic significance for outcomes and intracranial hypertension (ICH).

Material and methods

The study was conducted at the intensive care unit of the Burdenko Neurosurgery Center. Inclusion criteria: acute TBI, admission within 24 hours after injury and age 18—75 years. Exclusion criteria: atonic coma and decompensation of concomitant diseases.

Intensive care complied with national guidelines for the treatment of acute TBI [16]. Patients with severe and moderate TBI underwent invasive intracranial pressure (ICP) and hemodynamic monitoring, mechanical ventilation, sedation and analgesia and preventive measures for secondary brain injury.

We analyzed sIL-2R, IL-6, C-reactive protein and procalcitonin. Venous blood samples obtained through venipuncture in the morning for the first 10—14 days after TBI were analyzed regarding concentrations of inflammatory markers. Concentrations were determined by enzyme-linked immunosorbent assay (ELISA) with commercial test systems. Reference values: IL-6 — <5.9 pg/ml; sIL-2R — 158—623 pg/ml; CRP — < 5 mg/l; procalcitonin — < 0.05 ng/ml.

Data of prospective epidemiological surveillance in intensive care unit were used to analyze infectious complications in acute phase of TBI. Database included information about clinical status of patients, neurological status, signs of infection, implantation of invasive devices (ICP sensor, external ventricular drainage, central or peripheral venous access, arterial line, urethral catheter), cerebrospinal fluid leakage, mechanical ventilation and its characteristics (orotracheal intubation or tracheostomy tube, oxygen fraction, saturation) and other factors. Infection monitoring was carried out in accordance with definitions of the Centers for Disease Control/National Healthcare Safety Network (CDC/NHSN) [17].

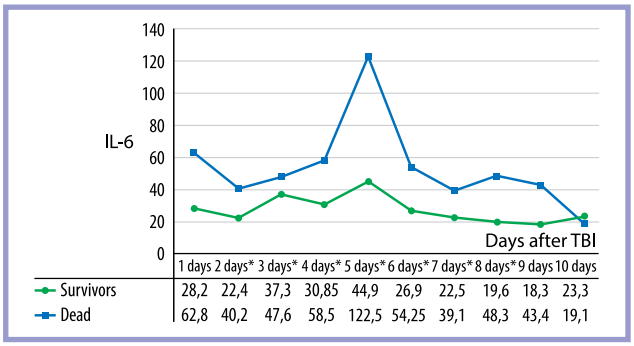

Fig. 1. **Serum interleukin-6 in survivors and dead patients. * — $p < 0.05$.**

Distribution normality was estimated using the Kolmogorov–Smirnov test. Data are presented as median and interquartile range. To compare data between survivors and deceased patients, the Mann–Whitney test was used. Differences were significant at $p<0.05$.

Results

The study included 74 patients (19 women, 55 men) with severe TBI. Mean age was 34.0±12.5 years (range 15—68). Eleven (14.9%) patients died.

IL-6 in acute period of TBI

On the 1st day, serum IL-6 was high without significant differences between survivors and deceased patients **(Fig. 1)**. This was associated with enhanced interleukin expression in TBI.

However, IL-6 concentration significantly decreased by the second day in patients with favorable outcomes **(Table 1**, **Fig. 2)** and remained high in fatal group. This is likely due to severe intracranial damage, as the main source of IL-6 in TBI are CNS cells (including microglia, astrocytes, and neurons).

After the 3rd day, we observed secondary increase of IL-6 in survivors that coincided with clinical manifestation of infectious complications. Peak concentration occurs on the 5th day after TBI (44.90 [18.80; 66.30]). Further

Table 1. **Interleukin-6 concentrations in survivors and fatal patients on the second day after TBI.**

Outcome	Mean	Median	Min	Max
Death (n=9)	98.96±106.2	40.2 [33.2; 144]	23.3	334
Survivors (n=42)	40.76±42	22.4 [9.3925; 62.125]	1.5	187

Table 2. **Soluble interleukin-2 receptor concentration in survivors and fatal patients on the fifth day after TBI.**

Outcome	Mean	Median	Min	Max
Death (*n*=8)	1811.12±1143.4	1660 [1043.5; 2604]	471	3.724
Survivors (*n*=53)	754.04±619.1	649 [428;796]	211	3.931

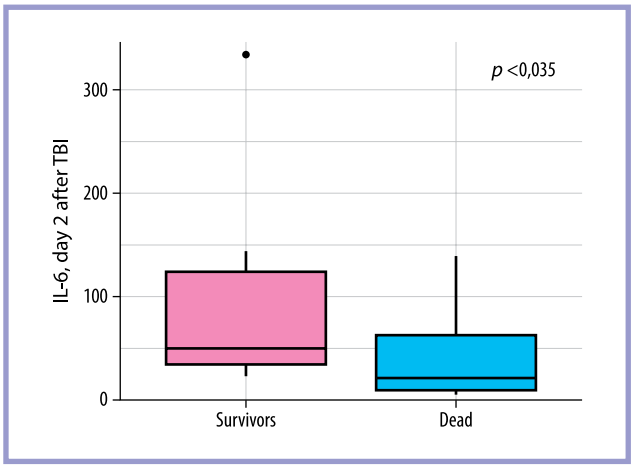

Fig. 2. **Interleukin-6 concentration in survivors and fatal patients on the 2nd day after TBI.**

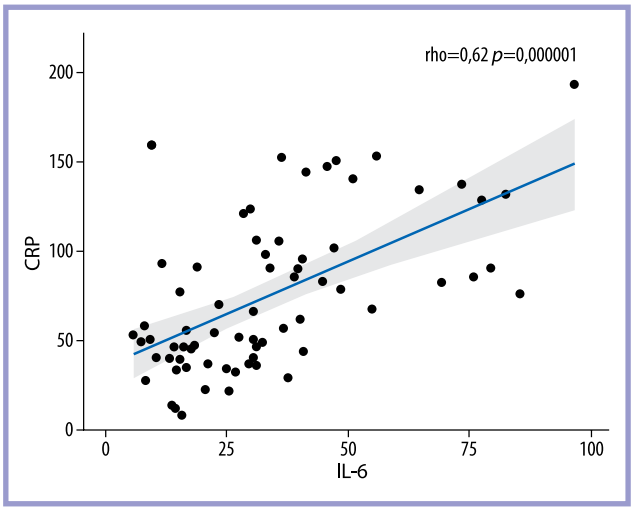

Fig. 3. **Correlation between interleukin-6 and C-reactive protein concentrations.**

changes of IL-6 concentrations in these patients are also explained by dynamics of infectious complications.

Furthermore, there was significant correlation between IL-6 and C-reactive protein **(Fig. 3)**. This may be explained by infectious complications, as well as IL-6-induced stimulation of C-reactive protein release.

After the 4th day, there were significant differences in IL-6 concentrations between survivors and dead patients. This is associated with cytokine storm following multiple organ failure and severe intracranial injuries, as well as addition of infectious complications.

sIL-2R in acute period of TBI

Analysis of sIL-2R concentration **(Fig. 4)** revealed significant differences on days 5 and 7 between survivors and deceased patients.

Dynamics of IL-2 in acute period of TBI is similar to IL-6 (increased concentration in response to TBI followed by decrease on day 2). After the third day, infectious complications increase serum IL-2 **(Table 2, Fig. 5)**. Peak concentration is also observed on the fifth day after TBI (649.00 [428.00; 796.00] in survivors and 1660.00 [1043.50; 2604.00] in fatal patients).

Correlation between inflammatory cytokines and intracranial hypertension in TBI

In survivors, correlation between IL-6 and intracranial hypertension was weak (Spearman's rank coefficient (rho)=0.29, p=0.03780). This may be explained by the absence of intractable intracranial hypertension observed in fatal patients.

In fatal patients, we observed correlation between intracranial pressure (ICP) and cytokine concentration. Elevated serum interleukins increase ICP and, consequently, decrease cerebral perfusion pressure **(Fig. 6)**. Thus, measurement of interleukin concentration within the first days after injury may be valuable to identify patients with high risk of intracranial hypertension.

Thus, IL-2 and IL-6 concentrations significantly increase on the first day in response to TBI and decrease later. Infectious complications occur after the 3rd day and increase serum interleukins. Peak interleukin concentrations are observed on the fifth day after TBI and significantly differ between survivors and non-survivors.

Discussion

Analysis of prognostic significance of early IL-6 dynamics demonstrates that the lack of differences between survivors and non-survivors within 24 hours reflects a universal systemic inflammatory response to massive brain injury. This is consistent with available data [12]. However, significant differences after 2 days are of fundamental importance. By this time, IL-6 decreases in survivors and remains persistently high in deceased patients. IL-6 concentration on the 2nd day was more than 1.8 times higher in deceased patients compared to survivors. Thus,

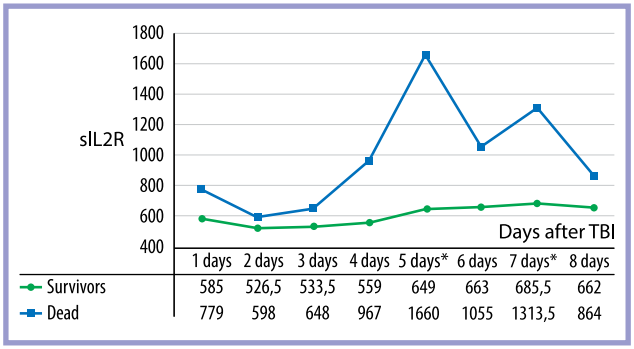

Fig. 4. **Concentration of soluble interleukin-2 receptor in survivors and fatal patients. * — $p<0.05$.**

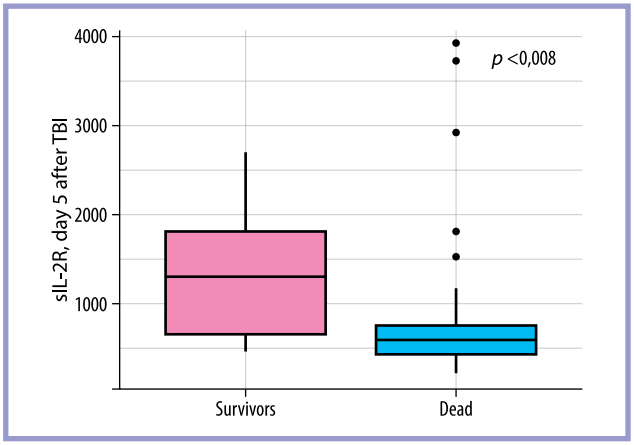

Fig. 5. **Distribution of soluble interleukin-2 receptor in survivors and fatal patients on the fifth day after TBI.**

one can consider early (48-hour) persistence of high serum IL-6 as a prognostic marker of uncontrolled neuroinflammation, likely due to large volume of damaged brain tissue. These data resolve contradictions between studies without correlation between serum IL-6 and outcomes [18] and studies demonstrating such a relationship [19]. Apparently, dynamics of this indicator is important instead of a single measurement.

Infectious complications and associated phenomenon of hyperinflammation are important for cytokine profile. A secondary rise in IL-6 on days 3—5 in survivors naturally coincides with manifestation of nosocomial infections. In deceased patients, a plateau of high concentrations after 4 days demonstrates synergistic effects of neuroinflammation and infection. The clearest marker of immune dysregulation was more than 2.5-fold increase in sIL-2R after 5 days in deceased patients. Concomitant IL-6 and sIL-2R peaks indicate transformation of protective inflammation into systemic hyperinflammatory syndrome with simultaneous involvement of innate and adaptive immune systems.

Clinical significance of interleukin monitoring is particularly relevant for critical illness requiring urgent individual monitoring and intensive care. In previous report, the authors described assessment of interleukins in a patient with severe TBI for rapid differentiation between sepsis, secondary adrenal insufficiency, and primary myocardial injury [20]. In this case, we observed a delayed response of C-reactive protein and procalcitonin to manifestation of infectious process. These markers increased only 48 hours after septic shock, whereas interleukins responded immediately to septicemia. These findings underscore the advantage of cytokines as markers for early diagnosis of complications, timely differentiation of causes of critical illness and selection of appropriate therapeutic strategy.

A key part of this study (direct correlation between IL-6 and ICP and inverse correlation with cerebral perfusion pressure in fatal patients) demonstrated pathogenetic association between IL-6 and ICP. This supports the hypothesis of direct involvement of IL-6 in pathogenesis of intracranial hypertension. Pathophysiological mechanism of this association may be mediated by increased blood-brain barrier permeability, stimulation of vasoactive molecule release and maintenance of proinflammatory

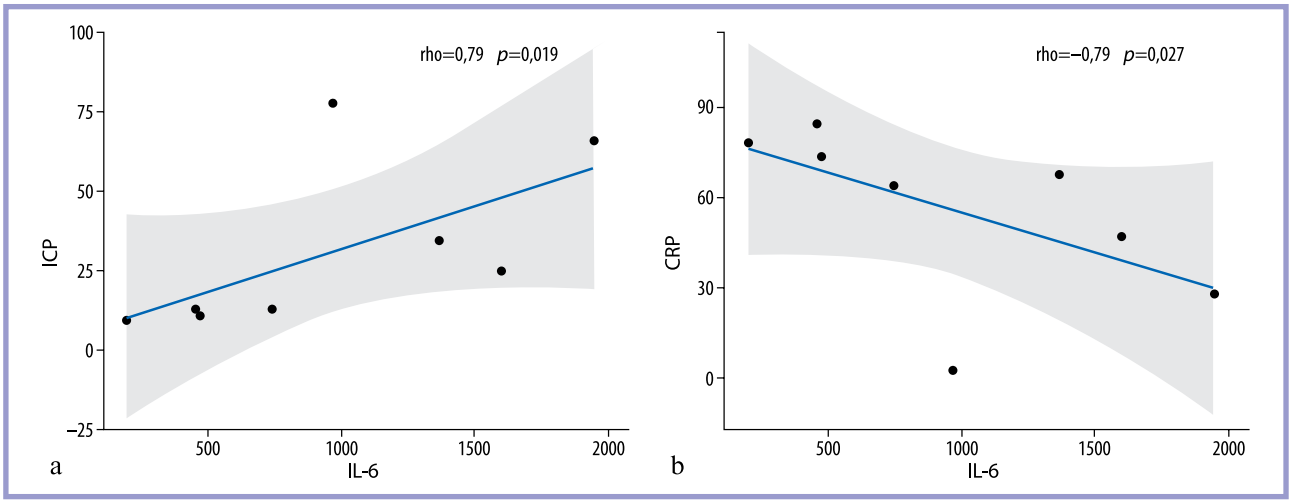

Fig. 6. **Relationship between interleukin-6 and intracranial pressure (a), interleukin-6 and cerebral perfusion pressure (b).**

glial phenotype. All these factors collectively lead to progressive edema. In survivors, this correlation was weak likely due to preserved autoregulatory mechanisms and effective therapeutic control of intracranial pressure.

The cutoff prognostic points are the 2nd day for IL-6 (no decrease) and the 5th day for sIL-2R (extreme increase). Patients with hyperinflammatory response may warrant more aggressive ICP control and early antibacterial therapy.

Combined therapy with cytokine antagonists is perspective and currently being studied in spinal cord injuries [21].

It is necessary to consider the limitations of this study when interpreting the results. A single-center design complicates generalizability of findings. Validation of results in multiple-center cohorts is required.

Conclusion

Acute phase of severe traumatic brain injury is accompanied by biphasic cytokine response. Early phase (2 days) is characterized by interleukin-6 increase in response to primary cerebral damage. The second phase (days 3—14) is associated with infectious complications and followed by elevation of serum soluble interleukin-2 and interleukin-6. Dynamics of interleukins is prognostically significant instead of absolute concentration. High serum interleukin-6 by 48 hours after injury indicates uncontrollable neuroinflammation and risk of unfavorable outcome. Peak (more than 2.5-fold) increase in soluble interleukin-2 receptor on day 5 is a marker for transformation of protective inflammation into systemic hyperinflammatory syndrome. Direct correlation between interleukin-6 and intracranial hypertension in fatal patients confirms pathogenetic role of this cytokine in secondary brain damage. Monitoring of interleukin-6 and soluble interleukin-2 receptor may enable timely identification of patients at high risk of fatal intracranial hypertension and provide personal approach to intensive care.

Author contribution:
Concept and design of the study — Sychev A.A.
Collection and analysis of data — Sychev A.A. , Baranich A.I.
Statistical analysis — Sychev A.A., Danilov G.V., Strunina Yu.V., Kakurin K.O.
Writing the text — Sychev A.A.
Editing — Sychev A.A., Savin A.V., Oshorov A.V., Kravchuk A.D.

The authors declare no conflicts of interests.

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COMMENT

The manuscript is devoted to a pressing issue in neurosurgery and intensive care (traumatic brain injury). Although various specialists have researched this problem for a long time, there are many unanswered pathophysiological and clinical questions.

Activation of immune, endocrine and autonomic nervous systems is essential for patients with any severe or critical illness. Outcomes of disease depend on adequate and balanced activation of these systems. TBI is a clear example of importance of a balanced response of immune, endocrine, and autonomic nervous systems. Paradoxical nature of situation is that routine assessment of these systems is not performed in neurosurgery and intensive care. Available Russian and foreign clinical guidelines for the management of patients with TBI lack aspects of diagnosis and treatment of immune, endocrine, or autonomic disorders.

The authors analyze two cytokines (interleukin-6 and soluble interleukin-2 receptor). The authors identified biphasic response of these cytokines and conducted appropriate correlation analysis of outcomes. Of course, their results cannot answer various questions regarding immune disorders in traumatic brain injury. However, these data clearly indicate involvement of immune system in pathogenesis and, possibly, thanatogenesis of traumatic brain injury. Furthermore, this study identifies a whole avenue for future research that will answer many unresolved pathogenetic and clinical questions regarding traumatic brain injury.

Popugaev K.A. (Moscow)