Chapter 5

Alterations in the Immune Response, Apoptosis and Synaptic Plasticity in Posttraumatic Stress Disorder: Molecular Indicators and Relation to Clinical Symptoms

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1. Introduction

Posttraumatic stress disorder (PTSD) (ICD-10 codes: F43.1, F62.0; DSM-IV-TR code: 309.81) [1, 2] is a complex severe and chronic psychiatric illness influenced by environmental and genetic factors [3-10]. PTSD is an anxiety disorder developed in a person experiencing, witnessing, or learning about an extreme physically or psychologically distressing event, associated with unprecedented violence [11, 12]. Traumatic events that can trigger PTSD include massacres, mass murder scenes, international, civil, political, ethnic and religious wars, genocides, natural and man-made disasters, criminal assaults, serious accidents, terrorist attacks, incarceration, trafficking, rape and other types of sexual assaults [12-17], life threatening illness and the sudden death of a loved one, serious medical illness, injury, surgery, hostage, kidnapping, difficult labors, etc [18-20]. Individuals who experience a trauma of this nature may develop symptoms that fall into three distinct clusters: re-experiencing phenomenon; avoidance and numbing; and autonomic hyperarousal. Symptoms usually begin within the first 3 months after the traumatic event and last for many years, although there may be a delay of months, or even years, before symptoms appear. PTSD patients are characterized by severe emotional state, sharp reduction in adaptive and information receiving abilities. They usually remain out of society, become drug addicted, alcoholic and often commit suicide [21-24]. Degrees of risk to develop PTSD from different traumatic events are presented in table 1.

It was shown that 37% of Cambodian refugees, 86% of women refugees in Kabul and Pakistan and 75% of Bosnian refugee women suffer from PTSD. In USA 60% of female rape sur-

vivors and 35% of UK adult rape victims are affected by PTSD. Similar to adults, some children, who witness or experience traumatic events, develop PTSD. Thus, in the USA 90-100% of children, who witness a parental homicide or sexual assault, develop PTSD, and in the UK 50% of sexually abused children are affected by this disorder [25-27].

Equally as staggering are statistics, which monitor the incidence of PTSD among combat veterans. Here, 30% of the American Vietnam veterans and 56% of Australia's Vietnam War veterans, 10% of Desert Storm veterans, 31% of Australia's Gulf War veterans, 6-11% of Afghanistan veterans and 12-20% of Iraq veterans in the US suffer from PTSD [25-28].

Statistical data also demonstrates that women are more than twice as likely to develop PTSD as men. Available data suggests that about 8% of men and 20% of women go on to develop PTSD [26, 29-31]. Is was also shown that PTSD is most often developed in representatives of national minorities, people surviving stressful events at list once in their life, as well as in people with low level of education, mental problems, having mentally ill family member or experiencing lack of support from their family members or friends [26, 29-31]. Currently, for about 7-8% of the USA population, 2-3% of the UK population, 6.4% of Australians and 3% of Cambodians suffer from PTSD [26-28].

Traumatic event	Degree of risk, %
Rape	49.0
Other types of sexual violence	23.7
Physical violence, severe beating	31.9
Accident and/or serious injuries	16.8-20.0
Stabbing, shooting	15.4
Sudden death of a family member or friend	14.3
Child's life-threatening illness	10.4
Murder, death or serious injury witness	7.3
Natural disasters - hurricane - tsunami - earthquake (adults/youths)	2.0-3.8 30.0-50.0 32.0-60.0 / 26.0-95.0
Man-made disasters	29.0
Terrorist attacks	28.0

Table 1. Risk for developing PTSD depending on traumatic event [25-27]

In Armenia PTSD is quite common as well, and is basically found among the descendants of Armenian Genocide victims, including current generation, combatants, refugees and victims of earthquake [32-40]. Thus, according to Goenjian et al, 73% among 1988 Spitak Earthquake

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survivors developed PTSD 4.5 years after the disaster [36]. In general, 10% of the world population is suffering from PTSD, and 70% is under the risk of developing PTSD [26-28].

Patients with PTSD have a reduced quality of life, an increased number of suicides and hospitalizations, high frequency of depressions, alcohol and drug abuse; social, family life and work become impossible.

Molecular mechanisms of generation and development of PTSD and their relation to the clinical psychopathologic criteria of this disorder are not clear yet. The lack of knowledge in this field significantly limits the development of effective therapeutic approaches for treatment of PTSD-affected subjects and prevention of further complications.

2. Neuroendocrine alterations in PTSD

PTSD is characterized by the central and autonomic nervous systems hyperarousal that is caused by functional changes in the limbic system, which is located between the brainstem and the cerebral cortex and coordinates their activities. This part of the brain regulates survival behaviors and emotional expression, being primarily concerned with tasks of survival such as eating, sexual reproduction and the instinctive defenses of fight and flight. It also plays a central role in memory processing. The hippocampus and amygdala, parts of the limbic system, regulate learning, memory, and emotion. The amygdala is important for the regulation of emotional memories, particularly for fear causing memories. It has been proven that amygdala is activated in the extreme situations. The hippocampus, on the contrary, is suppressed in these conditions. It has been shown that PTSD is characterized by functional hyperactivity of the amygdala and hypoactivity of the hippocampus [41-43].

A number of data suggests that alterations in the hypothalamic-pituitary-adrenal (HPA) axis and sympathoadrenal system (SAS) play a leading role in PTSD pathogenesis [13, 14, 44]. Thus, PTSD, as compared to norm, is characterized by low cortisol levels in plasma and saliva [45], whereas elevated levels of dehydroepiandrosterone (DHEA) and DHEA-sulfate are detected in this disorder [44-46]. Moreover, increased levels of corticotrophin realizing hormone positively correlated with the high levels of cortisol in cerebrospinal fluid of PTSD patients were observed [47]. Also, PTSD is characterized by increased glucocorticoid receptor sensitivity [48]. An increased levels of noradrenaline, neurotransmitter of central and peripheral sympathetic (adrenergic) nervous system, were detected in the cerebrospinal fluid of PTSD patients [49]. Noradrenaline is considered as one of the important mediators of central and peripheral autonomic stress response and has an important role in the regulation process of emotional memory [50]. It was also shown that high levels of noradrenalinefof the PTSD of the PTSD in urine positively correlate with the symptoms of PTSD [51]. In addition, the increased levels of dopamine, another mediator of the sympathetic nervous system and precursor of noradrenaline, were found in the blood and body fluids of PTSD-affected subjects [51-53].

There are several data indicating assumption that functional abnormalities in neuroendocrine system detected in PTSD patients are conditioned by hereditary factors [54]. Thus, as it

follows from table 2, PTSD is associated with the genetic mutations in a number of genes encoding neurotransmitters and hormones, their biosynthesis enzymes, receptors and transporters. Interestingly, 6 of the candidate genes for PTSD showed in the table 1 belong to the dopamine system. A positive association between the risk for development PTSD and TaqIA polymorphism of the dopamine D2 receptor gene was found [55]. Also, positive association was revealed between tandem repeat polymorphism of dopamine transporter gene and PTSD [56] as well as between dopamine D4 transporter gene long allele and severity of PTSD symptoms [57].

The γ-3 subunit of γ-aminobutyric acid, another mediator of nervous system, has also been studied in PSTD patients. Patients heterozygous for this gene have a higher probability of developing somatic symptoms of PTSD, sleeping disturbances, fair and depression than homozygous patients [58]. The studies of serotonin transporter gene showed that PTSD patients carrying one or two short alleles of this gene have a higher level of depression and suicide compared to carriers of long allele, which has more transcriptional power [59, 60]. The association of the serotonin transporter repeat polymorphism with PTSD was also described [61-63]. Interestingly, recent study of 200 individuals from 12 multigenerational families survived 1998 Spitak earthquake in Armenia demonstrated that PTSD is developing in those individuals, who carry mutations of tryptophan hydroxylase 1 and 2, the rate-limiting enzyme of serotonin biosynthesis [64].

Candidate gene	Chromosomal mapping	Source
Dopamine D2 receptor	11q23	[22, 55, 65]
Dopamine D4 receptor	11p15.5	[57]
Dopamine transporter type 1	5p15.3	[56, 66]
Serotonin transporter	17q11	[10, 60, 63, 67- 71]
Serotonin type-2A receptor	13q14-q21	[68]
Brain-derived neurotrophic factor	11p13	[72]
Neuropeptide Y	7p15.1	[73]
Glucocorticoid receptor	5q31.3	[74]
Dopamine beta-hydroxylase	9q34	[75]
Cannabinoid receptor	6q14-q15	[76]
γ-aminobutyric acid receptor (subunit α-2)	4p12	[77]
Catechol-O-methyltransferase	22q11	[78]
Tryptophan hydroxylase 1 Tryptophan hydroxylase 2	11p15.3-p.14 12q21.1	[64]

Table 2. PTSD-related changes in the neuroendocrine system

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3. Immune system alterations in PTSD

Promising studies suggest the involvement of alterations in the immune status [48, 79-86], particularly low-grade inflammatory reactions, in the pathogenesis of PTSD [87-97]. Thus, PTSD patients are characterized by hyperactivation of lymphocytes [80] and increased levels of lipopolysaccharide (LPS)-stimulated expression of interleukin (IL)-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ in immunocompetent cells [81, 82]. Segman et al detected over-expression of immune response-related genes in monocytes of PTSD-affected subjects [85]. Also, in chronic PTSD patients, as compared to norm, a decreased number of T-killer cells ($CD8^+$) [98, 99] and an increase number of T-helper cells ($CD4^+$) [98, 100] has been shown, whereas in PTSD patients immediately after a traumatic event a decreased number of T-helper cells was detected [99]. A number of experimental data indicates that natural killer cells' cytotoxicity in PTSD is lower than in norm [97, 99, 101-104], while the total number or these cells, as well as a number of $CD16^+$ and $CD56^+$ cells in their total population is higher than in norm [99, 104]. At the same time some studies show that natural killer cells' cytotoxicity in PTSD patients is higher than in healthy subjects [105, 106]. The analysis of the above mentioned data revealed altered cell-mediated immunity in PTSD patients and demonstrates that depending on traumatic event, duration and stage of the illness, these alterations may be either under- or over-represented [97, 107].

3.1. Cytokine network in PTSD

A number of studies have demonstrated changes in a functional state of cytokines and their receptors, important mediators and regulators of the immune response in PTSD-affected subjects. Here the increased blood levels of proinflammatory cytokines (e.g. IL-1β, IL-6, TNF-α, INF-γ) and decreased levels of anti-inflammatory cytokines (e.g. IL-4) are detected in chronic PTSD patients indicating the involvement of low-grade systemic inflammatory reactions in PTSD pathogenesis (table 3).

In our own study the levels of proinflammatory and chemotactic cytokines IL-1β, IL-6, TNF-α, IL-8 and MCP-1 in the blood serum of chronic PTSD patients (combat veterans) and age- and sex-matched healthy subjects (HS; a control group) were determined using enzyme-linked immunosorbent assay (ELISA). Assessment of possible correlation of the above mentioned parameters with each other and with the expression of PTSD clinical symptoms was also performed. The latest were evaluated using Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID PTSD module) [112] and Clinician-Administered PTSD Scale (CAPS) [113]. In particular, we assessed correlation between the levels of cytokines and the degree of expression of such PTSD clinical symptoms as persistent re-experiencing of the traumatic event (B cluster), persistent avoidance of stimuli associated with the trauma and emotional numbing (C cluster); persistent symptoms of increasing arousal (D cluster) [2]. In table 4 brief descriptions of the study groups is given. Table 5 demonstrates the individual symptom clusters (B, C, and D criteria), and total CAPS scores of PTSD-affected subjects involved in our study.

Chronic PTSD patients: group description	Changes in the blood levels of cytokines as compared to norm*	Source
Accidents survivors (n=13)	↑IL-1β, ↑IL-6, ↑TNF-α	[89]
Accident survivors (n=86)	↑IL-1β	[46]
Accidents survivors (n=14)	↑IL-1β, ↑TNF-α, ↓IL-4	[93]
Bosnian refugees (n=12)	↑IL-6	[108]
Combat veterans (n=19)	↑IL-1β, ↑IL-6, ↑TNF-α	[87]
Combat veterans (n=11)	↑IL-6, ↑TNF-α	[91]
Individuals abused in childhood (n=30)	↑INF-γ	[109]
Individuals abused in childhood (n=177)	↑TNF-α , ↓IL-4	[110]
Individuals exposed to different traumatic events (n=60)	↓IL-4	[97]
Individuals exposed to intimate partner violence (n=62)	↑IL-6, ↑TNF-α, ↑INF-γ	[111]

* - ↑ - above the norm; ↓ - below the norm.

Table 3. Changes in the blood levels of some cytokines in chronic PTSD patients

Data statistics include nonparametric Mann-Whitney U-test and correlation analysis with calculation of Spearman's rank correlation coefficient (Rs). Parts of this study have been published [114, 115].

The results obtained indicated that PTSD, as compared to norm, is characterized by increased levels of the mentioned above cytokines (Table 6), which is consistent with reports by other research groups (Table 3) [46, 87, 89, 91, 93, 108, 110, 111].

A significant correlation between the levels of IL-1β and IL-6 (Rs=0.45; p<0.003), as well as between IL-1β and MCP-1 (Rs=0.3; p<0.03) in PTSD patients was revealed, whereas no significant correlation between the levels of cytokines was observed in control group. Also, a significant positive correlation of IL-1β and IL-6 blood levels with PTSD symptoms within B, C and D criteria (CAPS scores) was detected. Thus, levels of IL-1β positively correlated with B frequency (Rs=0.004, p=0.007), C frequency, intensity, and frequency + intensity (Rs=0.4, p=0.009; Rs=0.30, p=0.035, r=0.36, p<0.02, respectively), frequency of B, C and D (Rs =0.37, p<0.02), total intensity of B, C and D (Rs=0.3, p<0.048) and total frequency + intensity of B, C and D (Rs=0.3, p<0.03). Blood levels of IL-6 positively correlated with cluster B frequency (Rs=0.3, p=0.048).

Our data provides further evidence on the association of chronic inflammation with PTSD and clearly demonstrates the interrelation between the expression of PTSD symptoms and inflammatory reactions. Alterations in the immune response in PTSD accompanied by low-grade systemic inflammation aggravate disease course and severity and contribute to development of complications. Thus, PTSD is often associated with autoimmune and

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inflammatory disorders such as rheumatoid arthritis, psoriasis and inflammatory bowel disease. Patients with PTSD are at a higher risk for diabetes mellitus and cardiovascular diseases (atherosclerosis, myocardial infarction) [116-123]. It is interesting that in peridontitis patients with PTSD higher expression of inflammatory processes was obtained than in those peridontitis patients, who were not affected by PTSD [88].

Study group	PTSD	HS
Total number (male/female)	120 (116/4)	80 (76/4)
Mean age (M±SD)	42 ± 11.3	39 ± 9.1
[Cortisol]* (M±SD), ng/ml	124 ± 47	145 ± 55
[DHEA]* (M±SD), ng/ml	13 ± 7	10 ± 5
[DHEA-sulfate]* (M±SD), µg/ml	1.8 ± 0.9	1.0 ± 0.5

* - measured in the blood serum

Table 4. Brief description of the study groups

Symptom clusters	Parameters	PTSD patients scores
B cluster	Frequency (0-20)	11.8±3.98
	Intensity (0-20)	11.6±3.46
	Frequency + Intensity (0-40)	23.4±7.02
C cluster	Frequency (0-28)	16.4±5.10
	Intensity (0-28)	14.8±4.96
	Frequency + Intensity (0-56)	31.2±9.85
D cluster	Frequency (0-20)	13.5±3.07
	Intensity (0-20)	12.2±2.52
	Frequency + Intensity (0-40)	25.7±5.30
B+C+D (Total)	Frequency (0-68)	41.7±9.85
	Intensity (0-68)	38.6±9.18
	Frequency + Intensity (0-136)	80.3±18.50

Table 5. The individual symptom clusters (B, C, and D criteria), total and overall CAPS scores (M±SD) of PTSD-affected subjects (Score ranges are indicated in parenthesis)

Study group	Cytokine	Level (M ± SD), pg/ml	P =
PTSD	IL-1β	8.2 ± 1.0	0.002
HS		5.1 ± 0.7	
PTSD	IL-6	19.0 ± 2.5	0.025
HS		16.0 ± 2.3	
PTSD	TNF-α	12.0 ± 1.6	0.049
HS		10.8 ± 1.4	
PTSD	IL-8	11.5 ± 1.5	0.022
HS		10.1 ± 1.3	
PTSD	MCP-1	223.3 ± 30.6	0.030
HS		187.2 ± 25.5	

Table 6. Comparative analysis of the blood serum levels of proinflammatory and chemotactic cytokines in patients with PTSD and HS

The pathological mechanisms of the development of inflammatory reactions in PTSD are not clear. However, it is obvious that neuroendocrine and immune impairments in PTSD are interrelated. It is well-established fact that the immune system functional activity is regulated by neurotransmitters and hormones, particularly those related to HPA axis and SAS. On the other hand, immune system mediators and their receptors on the immunocompetent cells may regulate the neuroendocrine system. In normal physiological conditions the immune, endocrine and nervous systems maintain homeostasis by controlling each other, thus developing adequate stress response [79, 124]. Changes in neuro-endocrine-immune interactions (influenced by either environmental or genetic factors) may result to abnormal response to stress and generation of PTSD. On the other hand, the action of cytokines, mediators of inflammation, is tightly coupled with physiological and pathophysiological reactions of the organism, and their important role is to coordinate the efforts of the immune, endocrine and nervous systems during the stress response [125-128]. This may represent one of the possible mechanisms responsible for increased cytokines levels and development of chronic inflammatory reactions in PTSD, the disease characterized by neuroimmune and endocrine alterations [82, 86, 129]. It connection with this it has to be also mentioned that a number of recent clinical and experimental data suggests the implication of low-grade systemic inflammatory reactions accompanied by increase in cytokines levels in pathogenesis of many psychiatric disorders [130-132].

3.2. The complement system in PTSD

The complement system is major effector of the immune response, which acts on the interface of innate and adaptive immunity, and is a key component and trigger of many immunoregulatory mechanisms. Activation of the complement generates opsonins, anaphylatoxins, and chemotaxins, mediators of inflammation and apoptosis (Figure 1)

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[133-135]. Changes in the functional activity of the complement cascade contribute to the pathology of many human diseases [136-138], including mental disorders [139-144], and are also detected during physiological stress [145-146]. The alterations in the complement cascade have been considered as indicator of the implication of inflammatory component in disease etiology, pathogenesis and/or progression [136-138].

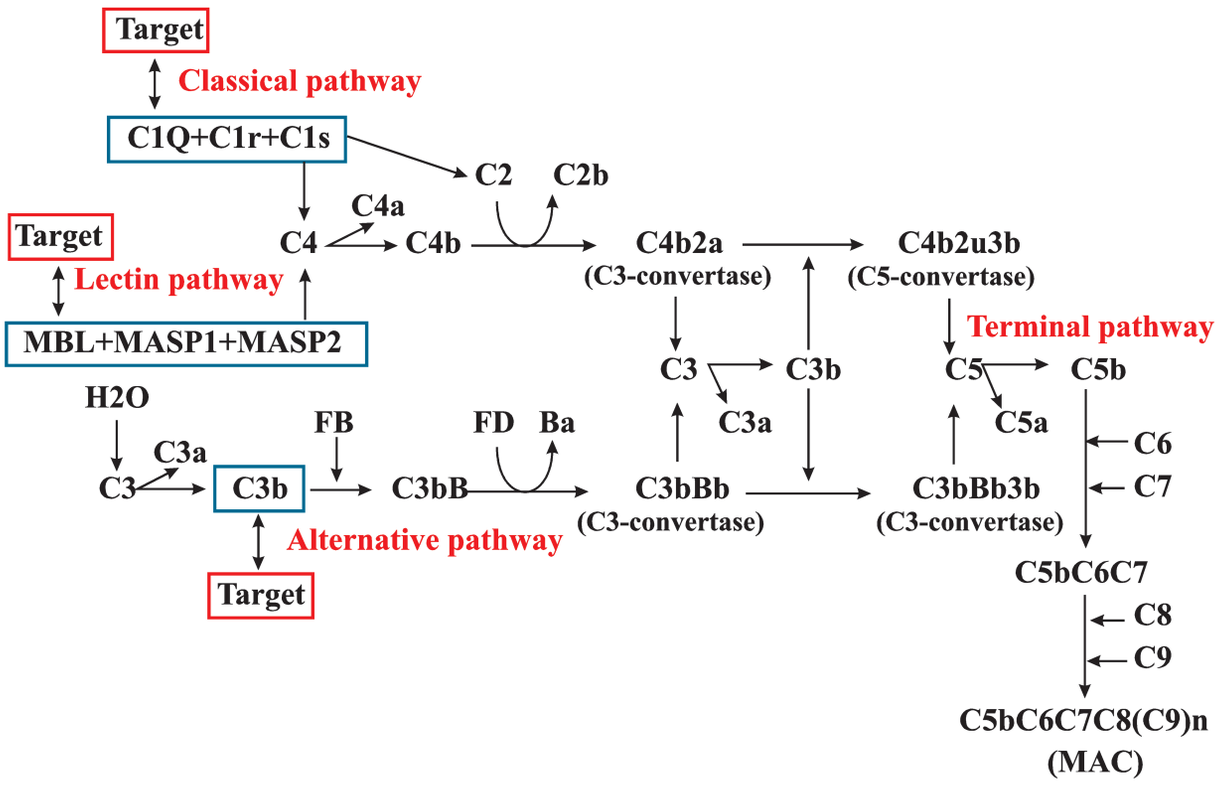

Figure 1. Complement activation pathways; C1Q, C1r, C1s – subunits of the complement C1 component; MBL - mannan-binding lectin; MASP1 - MBL-associated serine peptidase 1; MASP2 - MBL-associated serine peptidase 2; FD - factor D; FB - factor B; MAC – membrane attack complex.

The complement system with its central position in innate and adaptive immunity mediates a variety of effector functions. It consists of more than 30 circulating proteins, cell surface receptor and regulator proteins. It is a complex cascade involving proteolytic cleavage of serum glycoproteins often activated by cell receptors. This cascade ultimately results in induction of the antibody responses, inflammation, phagocyte chemotaxis, and opsonization of apoptotic and necrotic cells, facilitating their recognition, clearance, and lysis. Complement exhibits three activation pathways - classical, alternative, and lectin, initiated via separate mechanisms, and a single terminal pathway that results in a formation of the membrane attack complex (Figure 1) and subsequent cell lysis [133-135]. During the past decades it has become evident that dysfunction of complement contributes to the pathology of many human diseases [136-138], including mental disorders (schizophrenia, Alzheimer's disease, Huntington's and Pick's diseases) [139-142], and is also detected during physiological stress [145-146]. While, as it was already mentioned, PTSD-affected subjects showed a low-grade

systemic proinflammatory state, the complement system in PTSD has been never studied before.

In our study we assessed the functional activity of the complement cascade in PTSD by determining total hemolytic activities of its classical and alternative pathways, and hemolytic activities of its individual components, C1, C2, C3, C4, factor B and factor D, in the blood serum of chronic PTSD patients (combat veterans) and HS (tables 4, 5). C1, C2 and C4 are main components of the classical pathway, factor B and factor D are essential components of the alternative pathway, and C3 is the initial point for the alternative pathway and a converge point of all three complement activation pathways, starting up for the terminal pathway (Figure 1) [133-135]. In addition, correlation study between all measured parameters was also performed. Hemolytic activities of the complement classical and alternative pathways (CH50 and AH50, respectively) and of the complement components C1 (C1H50), C2 (C2H50), C3 (C3H50), C4 (C4H50), factor B (fBH50), and factor D (fDH50) in the blood serum of PTSD-affected and healthy subjects were measured by application of the earlier developed methods [147, 148]. Data was analyzed by Student's unpaired two-tailed t-test and Pearson's correlation analysis including calculation of relevant correlation coefficient (r). Parts of this study have been published [149-152].

The results obtained are presented in table 7. According to the results obtained, mean values of serum CH50, C1H50, C2H50 and C4H50 in PTSD patients were significantly 2.1, 1.34, 1.2 and 1.6 times significantly higher than in case of HS ($p<0.05$). On the contrary, mean values of serum C3H50, AH50, fBH50, and fDH50 in PTSD patients were 1.5, 1.7, 1.6, and 2.3 times significantly lower as compared to HS ($p<0.05$). Correlation analysis also demonstrated that in PTSD affected subjects C1H50 is significantly correlated with C2H50 ($r=-0.375$, $p<0.04$), C3H50 is significantly correlated with C1H50, C2H50 and C4H50 and AH50 ($r=0.53$, $p<0.037$; $r=0.72$, $p=0.002$; $r=0.5$, $p=0.05$; $r=0.57$, $p=0.027$, respectively). No significant correlation between the above-mentioned parameters was detected in the HS group ($p>0.05$).

Hemolytic activity, U/ml*	PTSD (M ± SD)	HS (M ± SD)	P =
CH50	375.00 ± 164.40	176.00 ± 88.50	0.0002
C1H50	92.21 ± 52.83	68.80 ± 37.39	0.0400
C2H50	67.60 ± 35.10	58.80 ± 8.80	0.0450
C3H50	37.57 ± 16.26	55.92 ± 28.60	0.0300
C4H50	60.10 ± 28.42	36.64 ± 20.31	0.0300
AH50	52.30 ± 18.17	87.60 ± 9.80	0.0001
fBH50	40.80 ± 14.30	65.2 ± 34.1	0.0200
fBH50	71.70 ± 15.98	163.70 ± 70.58	0.0010

* - one unit (U) of hemolytic activity is defined as an amount of serum that causes a 50% hemolysis of erythrocytes in a reaction mixture.

Table 7. Functional state of the complement system in PTSD patients and HS

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The results obtained in our study clearly demonstrated that pathogenesis of PTSD is characterized by complement dysfunction including hyperactivation state of the complement classical pathway and hypoactivation state of the complement alternative pathway. The alternative pathway of complement is activated following spontaneous hydrolysis of the thioester bond of native C3, resulting into binding of factor B, which is cleaved by factor D, generating the efficient alternative pathway C3 convertase C3bBb. Multifunctional complement protein C3 is the initial point of the alternative pathway, and, at the same time, a converge point of all three complement activation pathways, i.e. starting point for the terminal pathway [93, 135, 153]. Hypoactivation state of the alternative pathway together with decreased activity of the complement C3 component, detected in PTSD affected subjects, probably reflects depletion of the C3 component due to its overutilization through the terminal pathway. This suggestion is convenient with correlation data indicating positive correlation between CH50 and C3H50 and absence of any correlation between AH50 and fBH50, and AH50 and fDH50 in PTSD affected subjects. Thus, it is obvious that the alternative pathway in PTSD is suppressed on the initial stage of its activation, and that PTSD is also characterized by overactivated terminal complement pathway. On the other hand, absence of correlation between AH50 and CH50 suggests that alterations in activities of the classical and the alternative complement pathways in PTSD are not interdependent.

As it was mentioned above, alterations in the complement cascade have been considered as indicator of the implication of inflammatory component in disease etiology, pathogenesis and/or progression [136-138]. Our study demonstrates that PTSD is associated with dysfunction of the complement system, and reveals the altered chains of the complement cascade. The results obtained provide further evidence on the involvement of the inflammatory component in pathogenesis of PTSD. Here we hypothesize that neuroendocrine mechanisms related to PTSD modulating the immune function might affect the initial steps in the inflammatory cascade and thus influence alterations in the functional activity of the major mediator of the inflammatory response, the complement system. However, to address molecular mechanisms responsible for the complement dysfunction in PTSD as well as their role in PTSD pathogenesis further studies are needed.

3.3. Immune complexes in PTSD

Formation of immune complexes (IC) is a normal physiological reaction of organism to foreign or autoantigen. IC may interact with both humoral and cellular components of the immune recognition system, activate the complement cascade, and thus affect the immune response on multiple levels [154-156]. In healthy conditions IC are easily eliminating from circulation through complement deposition, followed by their opsonization, phagocytosis, and further processing by proteases [154, 156-158]. In pathologic conditions inappropriate clearance or deposition of IC result in increased levels of IC in circulation. Circulating IC may deposit in endothelial or vascular structures provoking prolonged inflammatory response by permanent activation of the complement cascade through the classical pathway, generation of cytotoxic agents and tissue damage [159-163]. Deposition of IC is a prominent feature of many diseases [162-164] including those characterized by low-grade systemic in-

flammation, such as schizophrenia [144], diabetes mellitus [165, 166], ischemic and hemorrhagic stroke [167-169].

In our own study we, for the first time, determined total levels of IC as well as the levels of IC containing activation products of the complement system, C1q- and C3d-IC, in the blood serum of chronic PTSD patients (combat veterans) and HS. Brief characteristic of study groups is given in tables 3, 4. Total levels of IC were measured by a previously published spectrophotometric method and expressed in absorbency units at 280 nm (A_{280}) [167]; C1q- and C3d-IC were measured by ELISA. Data was analyzed by Student's unpaired two-tailed t-test and Pearson's correlation analysis including calculation of relevant correlation coefficient (r). Parts of this study have been published [149, 150, 170].

According to the results obtained, PTSD-patients comparing to HS are characterized by significantly increased serum levels of total IC as well as C1q- and C3d-IC. Thus, the mean level of total IC in PTSD patients was 1.5 times higher than in HS (p=0.0055) and the levels of C1q-IC, and C3d-IC were 1.7 (p=0.024) and 1.6 times (p=0.0004), respectively, higher as compared to HS. The results obtained are summarized in table 8.

[IC], (M±SD)	Study group		P =
	PTSD	HS	
[Total IC], A_{280}	0.18 ± 0.1	0.12 ± 0.03	0.0055
[C1q-IC], μg/ml (M±SD)	44.6 ± 37.67	26.28 ± 16.33	0.024
[C3d-IC], μg/ml (M±SD)	29.75 ± 21.91	18.67 ± 8.22	0.0004

Table 8. Serum levels of the total IC, C1q-IC and C3d-IC in PTSD patients and HS

In addition, a significant positive correlation between the levels of C1q- and C3d-IC (r=0.32; p<0.03) was detected in PTSD patients affected subjects. Moreover, in patients with PTSD we also revealed a significant positive correlation between the total levels of IC and hemolytic activity of the classical complement pathway. This finding indicates that increased total levels of IC in circulation may be responsible for hyperactivation of the classical complement cascade detected in PTSD [149-152, 170].

The increased blood levels of C1q-IC in PTSD provide further evidence for this suggestion. C1q-IC contain C1q subunit of the complement protein C1, and binding of IC to C1q initiates activation of the classical complement cascade (Figure 1) [133-135].

C3d-IC contain activation cleavage products of the complement C3 protein, opsonins C3b, iC3b and C3dg. These entire products contain "d"-terminal fragment of the C3 polypeptide chain. In healthy conditions C3d-IC are eliminated from the blood through interaction with the complement receptors on monocytes, neutrophils and erythrocytes. Monocytes and neutrophils subject C3d-IC to phagocytosis, and erythrocytes transfer them to liver and spleen for further phagocytosis by macrophages. Increased blood levels of C3d-IC suggest about al-

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terations in mechanisms responsible for their recognition and clearance by the above mentioned cells. High levels of C3d-IC result in hyper-production of antibodies, because binding of C3d-IC to type-2 complement receptors (CR2) on the surface of B-lymphocytes induces the production of immunoglobulins by these cells [154, 156-158]. Therefore, our results indicate that PTSD is characterized by altered mechanisms of IC recognition and clearance, which may be responsible for the increased classical pathway functional activity, chronic activation of the immune system and systemic inflammation.

3.4. Interrelation between inflammatory response, apoptosis and synaptic plasticity in PTSD

As it was already mentioned, the molecular pathomechanisms responsible for development of inflammatory reactions in PTSD are yet unclear, which limits the progress in development of the efficient measures of PTSD rehabilitation therapy and prevention of its complications. On the other hand, it is known that apoptosis plays an important role in down-regulation of the inflammatory response by reducing the lifespan of activated immunocompetent cells [171-173]. Therefore, we proposed that one of the factors contributing to PTSD-associated inflammation may be apoptotic dysfunction as it was observed in case of other disorders like familial Mediterranean fever [174], inflammatory bowel disease [175], systemic inflammatory response syndrome [176], pulmonary hemorrhage or endotoxemia [177], etc.

On the third though, apoptosis is considered as the important regulator of synaptic plasticity. Apoptotic alterations have a significant input in synaptic dysfunction and lead to changes in structural and functional integrity of neuronal circuits [178-180]. Therefore, apoptosis may be also responsible for altered synaptic plasticity in PTSD [181] resulting in cognitive impairments and development of depressions in PTSD affected subjects [182-184].

To check our hypotheses, in the blood serum of patients with PTSD, in comparison to HS the levels of marker proteins for apoptosis and synaptic plasticity, annexin-A5 [185] and complexin-2 [186], respectively, and the inflammatory marker, TNF-α, were determined by ELISA. The analysis of correlation between these parameters was performed. Brief characteristic of study groups is given in tables 4, 5. Data statistics include nonparametric Mann-Whitney U-test and correlation analysis with calculation of Spearman's rank correlation coefficient (Rs). The results presented below have not been published yet.

According to the results obtained, the levels of both annexin-A5 and complexin-2 in PTSD patients were significantly 2.34 ($p=0.0001$) and 1.21 ($p=0.03$) times, respectively, lower than in case of HS (table 9). In addition, a significant positive correlation between the levels of annexin-A5 and complexin-2 ($Rs=0.38$, $p=0.045$), on the one hand, and a significant negative correlation between the levels of annexin-A5 and the increased levels of TNF-α ($Rs= -0.35$, $p=0.047$), on the other hand, were detected in PTSD.

No statistical significant correlation was observed between these parameters in case of HS.

Study group	[Annexin-A5], ng/ml	P =	[Complexin-2], pg/ml	P =
PTSD	0.82 ± 0.70	0.0001	121.5 ± 41.20	0.03
HS	1.92 ± 1.05		146.9 ± 56.64	

Table 9. The levels of annexin A5 and complexin-2 (M ± SD) in PTSD patients and HS

Our results demonstrated that PTSD is characterized by the decreased blood levels of the apoptotic marker circulating annexin A5 indicating association of apoptosis hypofunction with this disorder.

On the base of the results obtained we suggest that PTSD is characterized by low rate of apoptosis associated with the defects in synaptic plasticity and that anomalous apoptosis may also represent one of the factors responsible for development of PTSD-associated chronic inflammation. This suggestion is confirmed by recent findings indicating the increased levels of leukocytes in the blood of chronic PTSD patients [48, 93, 94].

4. Conclusion

The results presented in this chapter provide evidence on implication of altered immune response, particularly low-grade systemic inflammation, in pathogenesis of PTSD.

In particular, we demonstrated that chronic PTSD is characterized by increased blood levels of proinflammatory and chemotactic cytokines, IL-1β, IL-6, TNF-α and MCP-1, IL-8, respectively. Here, the increased levels of IL-1β and IL-6 positively correlate with the degree of expression of clinically significant symptoms of this disease, which indicate that these cytokines may be considered as new therapeutic targets for PTSD treatment. In addition, we demonstrated that chronic PTSD is characterized by altered mechanisms of IC recognition and clearance resulting in the increased levels of total IC, as well as C1q-IC and C3d-IC in circulation. Furthermore, our results showed that chronic PTSD is characterized by alterations in functional activity of the complement pathways including hyperactivation state of the classical and terminal pathways, hypoactivation state of the alternative pathway and deficiency of the C3 complement protein. Here, the data obtained suggests that hyperactivation of the classical complement pathway is induced by the increased levels of IC, particularly C1q-IC, in circulation. Regarding the alternative pathway, our results clearly demonstrated that it is suppressed at the initial stage of activation and that decreased activity of this pathway in PTSD is stipulated by decreased activities of its components, factor B and factor D, and deficiency of the protein C3, a key component of the complement cascade.

In summery, we concluded that changes in functional activities of the proinflammatory and chemotactic cytokines and complement cascade, as well as disturbances in the IC recognition and clearance processes are implicated in pathogenesis of chronic PTSD.

Another important conclusion that can be drawn from the results of our study is that pathogenesis of chronic PTSD is characterized by low rate of apoptosis associated with the defects

in synaptic plasticity, and that anomalous apoptosis may represent one of the factors responsible for development of PTSD-associated chronic inflammation.

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