

## CHANGES OF IMMUNE STATUS IN PATIENTS WITH MIXED ANXIETY AND DEPRESSIVE DISORDER AND HERPETIC VIRAL INFECTION

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**Abstract.** *Depression and anxiety are the most common mental disorders worldwide. A number of researchers have described a correlation between immune, limbic and endocrine systems and their role in the development of anxiety – depressive disorder. However, a more detailed examination of this correlation is yet to be performed. This study was conducted to examine immunological disorders' impact on cytomegalovirus (CMV), Epstein – Barr virus and herpes simplex virus antibodies' production; to evaluate antiviral antibodies' level impact on an immune status; to estimate an amount of strong systemic correlation between immunological parameters. Blood samples of 40 patients with Mixed Anxiety and Depressive Disorder were explored, immunological and "infectious" statuses were evaluated. Therefore, the variation in titer of antibodies to cytomegalovirus, Epstein – Barr virus and Herpes Simplex Virus with respect to changes of immunological parameters was detected. Additionally, taking the above into account, many strong correlations between HSV and CMV and immune system (48 and 32 respectively) suggest that there is high – level immunity against these viruses. In contrast, only 3 correlations between Epstein – Barr Virus and immunological parameters indicate that poor immune response is usual to this virus. The strong correlations between HSV and EBV and immune response among patients with proved diagnosis of MADD possibly indicate that mental condition is able to impact on human immune status.*

**Keywords:** *anxiety, depression, immunity, herpes simplex virus, cytomegalovirus, Epstein – Barr virus.*

**Introduction.** According to epidemiologic data, depression and anxiety disorders are the most common mental disorders [9]. The data indicates that the prevalence of anxiety – depressive disorders worldwide is between 4,4 and 20 % among all population (between 350 million and 1,5 billion people) [1]. The new evidence has shown that the number of patients with anxiety and depressive disorders was higher than the number of patients with other mental disorders. The prevalence among all population was about 10 %, and 30% of patients in ambulatory medical institutions [8]. At the same time, more consistent data about Mixed Anxiety and Depressive Disorder's (MADD) prevalence is yet to be researched.

MADD is characterized by bad mood, worries, feeling of impending disaster, death or incurable disease, feeling of anxiety. ICD – 10 classifies this condition as "Mixed anxiety and depressive disorder", code F41.2.

There are several concepts concerning the association between human psyche and human immune system. A significant correlation between immune, limbic and endocrine systems and its role in the development of anxiety – depressive disorder was described by a number of scientists [2]. Furthermore, the data has shown a bidirectional regulation of immune and mental systems. In fact, a chronic stress, known as a predictor of many mental disorders, is associated with a high production of inflammatory mediators (cyto-

kines) and increased risk of infections and chronic total inflammation. Furthermore, an HPA – axis, activated by inflammatory cytokines, triggers a production of kynurenine. Kynurenine is one of the main risk factors of anxiety and depression development [3]. Moreover, neuroinflammation, provoked by the impact of stressors, is detected by many researchers. Thus, the sympathetic system is directly related to HPA – axis functioning [10]. Normally, under the impact of stressors the sympathetic system starts a high production of noradrenaline, which, in turn, stimulates progenitor immune cells and increase granulocytes and monocytes blood level [7]. Modern research technologies allow to study a possible correlation between mental misadaptation and immune and endocrine system [4]. However, a number of current studies are still unable to clarify the interaction of all these factors. Apart from this, the comprehensive description of pathological mechanisms is also necessary. Therefore, further studies are to be performed.

Likewise, current studies are unable to exclude an infectious part of anxiety and depression pathogenesis. Apparently, a significant increase of anxiety and depression manifestation, caused by herpes simplex virus, type 6B (HSV), was reported by colleagues [6]. In addition, an HSV was detected in respiratory tract and olfactory bulbs in brain, known also as immune organ. An olfactory bulbs' enlargement was detected among experimental mice, infected by HVS type 6B. Apart from this, further tail – suspension test, when infected mice stayed immobile, was interpreted as a significant mark of depression [5, 6]. Our research is to study a possible association of anxious and depressive symptoms and immune changes.

All in all, the existing studies have failed to explain an exact association between anxiety and depression and contamination by NVS, Epstein – Barr Virus and CMV. Furthermore, immunological disorders' impact on cytomegalovirus (CMV), Epstein – Barr virus (EBV) and herpes simplex virus antibodies' production was rarely analyzed in previous studies. Thus, the aim of this study is to examine an impact of cytomegalovirus's (CMV), Epstein – Barr virus's and herpes

simplex virus's presence on an immune status and to evaluate a correlation between immunological parameters and virus presence.

**Design and methods.** This study was retrospective and individually randomized. All participants gave written informed consent. We recruited 40 participants, both men and women, aged 18 – 45, from day patient department of Voronezh Regional Clinical Psychoneurological Dispensary, with the diagnosis of Mixed Anxiety and Depressive Disorder (MADD) and with no cardiovascular, respiratory, urinary, endocrine or oncological somatic anamnesis. The anamnesis and complaints were examined. All participants were asked to fill in a Hamilton Depression and Anxiety Rating Scale to prove the psychiatric diagnosis of MADD. We measured blood samples at the Screening Visit of the study to evaluate an immune status (CD3 – cells, CD4 – T – helpers, CD8 – cytotoxic cells, CD19 – B – cells, CD16+56 – N – killers, CD 28 +/- - lymphocytes, CD 25 +/-, CD8+16 – cells; adherent phagocytosis assay) and infectious status (determination of IgG, IgA, IgM of cytomegalovirus, Epstein – Barr virus and herpes simplex virus in blood serum by radial immunodiffusion method) of all participants. We used such approved laboratory materials and gadgets as vacutainer serum tubes 2 ml, vacutainer plasma tubes K3 2 ml, vacutainer hematocrit tubes K2 – EDTA 2 ml, photometer Zenyth 340, Zenyth 340 ST, Zenyth 340 RT, Zenyth 340 S, cytofluorometer NAVIOS. The measurements were consolidated and data-processed by estimation of normality of distribution, determining mathematical expectation and its errors, evaluation of statistically significant correlations.

**Results.** 40 male and female participants, aged 18 – 45, from day patient department of Voronezh Regional Clinical Psychoneurological Dispensary were included in the study. All the patients were diagnosed with Mixed Anxiety and Depressive Disorder (MADD) and had no cardiovascular, respiratory, urinary, endocrine or oncological somatic anamnesis. Three most important components of immune system were evaluated: humoral, cellular and phagocytic. Additionally, the evaluation of immune status (CD3 – cells, CD4 – T – helpers, CD8 – cytotoxic cells, CD19 – B –

cells, CD16+56 – N – killers, CD 28 +/- - lymphocytes, CD 25 +/-, CD8+16 – cells; adherent phagocytosis assay) and infectious status (determination of IgG, IgA, IgM of cytomegalovirus, Epstein – Barr virus and herpes simplex virus in blood serum by radial immunodiffusion method) was completed. The presence of all herpetic viruses was determined among all included patients. Thus, antibodies to all herpetic viruses (CMV, EBV and HSV) were determined in 30% of patients; antibodies to Epstein-Barr Virus were found in 100% of subjects; 60% of subjects were carriers of cytomegalovirus; antibodies to herpes simplex virus were detected in 70% of patients.

Our data indicates, that there are many strong associations between antibodies for HSV and immune cells: a positive statistically significant correlation with CD3+, CD38+ (T-cells) ( $r=0,46$ ); a negative statistically significant correlation with CD3+, CD8+ (T-cytotoxic lymphocytes) ( $r=-0,67$ ); a negative statistically significant correlation with CD8+(T-suppressors) ( $r=-0,37$ ); a negative statistically significant correlation with CD16+(NK-cells) ( $r=-0,37$ ); a negative statistically significant correlation with colony – enhancing factor ( $r=-0,40$ ); a negative statistically significant correlation with phagocytic index ( $r=-0,66$ ); a positive statistically significant correlation with macrophage activity (NBT-Test) ( $r=0,82$ ). Furthermore, the titer of CMV antibodies was negatively significantly correlated CD3+, CD8+ ( $r=-0,37$ ); also, has a negative statistically significant correlation with CD8+ ( $r=-0,54$ ); a negative statistically significant correlation with CD16+(NK-cells)

( $r=-0,71$ ); a negative statistically significant correlation with phagocytic index ( $r=-0,72$ ).

The similar study of possible correlations indicated that antibodies to Epstein-Barr Virus positively significantly correlated with macrophage activity (NBT-Test) ( $r=0,57$ ) as well.

**Discussion.** Our findings demonstrate that the variation in titer of antibodies to cytomegalovirus, Epstein – Barr virus and Herpes Simplex Virus with respect to changes of immunological parameters was detected. The total number of strong correlations between HSV and immunological parameters was 48; the total number of strong correlations between CMV and immune system was 32. On the other hand, the sum of strong correlations between EBV and immune system parameters was only 3. Additionally, taking the above into account, strong correlations between HSV and CMV and immune system (48 and 32 respectively) suggest that there is high – level immunity against these viruses. In contrast, only 3 correlations between Epstein – Barr Virus and immunological parameters indicate that poor immune response is usual to this virus.

**Conclusion.** Our research results allowed to suggest an unspecified association between a human immune system and human mentality. All proved strong correlations between HSV and EBV and immune response among patients with proved diagnosis of MADD possibly indicate that mental condition is able to influence human immune status. However, these are preliminary findings that lead to further research.

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## ИЗМЕНЕНИЯ ИММУННОГО СТАТУСА У БОЛЬНЫХ СО СМЕШАННЫМ ТРЕВОЖНО-ДЕПРЕССИВНЫМ РАССТРОЙСТВОМ И ГЕРПЕТИЧЕСКОЙ ВИРУСНОЙ ИНФЕКЦИЕЙ

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***Аннотация.** Депрессия и тревоги являются одними из самых распространенных психических заболеваний во всем мире. Целым рядом авторов была описана связь между психикой и иммунной системой человека, при этом требуется более подробное изучение роли этой связи. Наше исследование было проведено с целью изучения влияния иммунологических расстройств на образование антител к цитомегаловирусу, вирусу Эпштейн – Барра и вирусу простого герпеса человека, оценки влияния концентрации антивирусных антител на иммунный статус и определения количества сильных внутрисистемных корреляционных связей между иммунными показателями. Мы исследовали образцы крови 40 участников с диагнозом «Смешанное тревожное и депрессивное расстройство». Кроме того, были оценены иммунологический статус пациентов и носительство ими антител к вирусам герпесной группы. В результате была установлена зависимость изменения титров антител к цитомегаловирусу, вирусу Эпштейн – Барра и вирусу простого герпеса человека от нарушения иммунологических показателей. Кроме того, на основе результатов корреляционного анализа, было определено количество сильных корреляционных внутрисистемных связей при изучении иммунной картины инфицирования вирусом простого герпеса человека – 48 связей. Аналогичная оценка связи инфицирования цитомегаловирусом и иммунного статуса говорит о наличии 32 сильных связей. Такое количество сильных связей свидетельствует о формировании напряженного иммунитета в отношении вышеуказанных вирусов. С другой стороны, количество сильных корреляционных связей между инфицированием вирусом Эпштейн – Барра и иммунным состоянием было всего 3, что позволяет говорить о формировании слабого иммунитета к инфицированию этим вирусом.*

*Собранные данные свидетельствуют о существовании связи иммунной системы с психикой человека. Установленные сильные связи между титрами антител к цитомегаловирусу, вирусу простого герпеса человека, вирусу Эпштейн – Барра и выраженностью иммунологических показателей говорят о возможном влиянии психического состояния на иммунный статус человека.*

***Ключевые слова:** тревога, депрессия, иммунитет, вирус простого герпеса, цитомегаловирус, вирус Эпштейн – Барра.*