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Review

Flavivirus Encephalitis and Immune Response

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Abstract

Tick-borne encephalitis (TBE) is a severe and potentially fatal neurological disease among population of endemic areas from northern China and Japan, through Russia to more than 16 European countries [1]. Beginning from 1970s a 400% increase in TBE morbidity had been registered. One of the striking epidemiological features of TBE has been periodic variation in the occurrence and severity of TBE infections in different endemic regions from Far Eastern Russia to Europe. Peak values last 1 -2 years and trough values last for 6-7 years separated by intervals of gradual transition over 1-5 years. Last maximal TBE morbidity rate had been observed in 1999 with 11,356 TBE cases in Eurasia (www.tbe-info.com) (and among them 9,955 – in Russia alone). Despite the availability of effective vaccine, an average immunization rate in endemic regions of Russia do not exceed a few percent (5-7%), in Europe vary from 6% in Baltics to 13% in Germany and 88% in Austria. Vaccines are based on Far Eastern and European strains of TBE virus in spite of evident prevalence of Siberian genetic subtype in endemic regions of Russia and surrounding countries. Moreover, TBE is an immunopathological disease, where the inflammatory $CD8^+$ T cell-mediated reactions contribute to neuronal damage and could lead to a fatal outcome [2]. Our report summarizes the available data on the TBEV influence on immune response impairments with focus on comparison of cytokine genes expression levels after infection and immunization. IJBM 2011; 1(4):231-235.

Key words: *Tick-borne encephalitis, Immune response, cytokines.*

TBEV belongs to the family Flaviviridae, genus Flavivirus, a group of tick-borne viruses in mammals [3]. Maximal TBE morbidity rate had been registered in 1956 (5,163 cases) and 1964 (5,205 incidences). Then until 1974 TBE prevalence gradually declined to 1,119 cases. During 1976-1989 an average annual morbidity level in Europe and Russia was 2,755 and between 1990 and 2007 — an average of 8,755 reported cases of TBE per year . In 1999 11,356 cases of TBE in Eurasia (www.tbe-info.com) (and among them 9,955 – in Russia alone) render the highest sickness level in all endemic regions. However, these underestimations of TBE rate are based on confirmed hospitalized cases of severe encephalitis or meningoencephalitis and comprise nearly 20-30% of real TBEV infection prevalence among populations from endemic regions. The figures are second only to those for Japanese encephalitis [1]. The leading areas, based on the TBE incidence, included the Urals, the East and West Siberian regions. These regions revealed 93% of all the registered TBE cases in the country. During the past decade, TBE cases were identified in populations of previously unaffected areas: Penza, Yaroslavl, Magadan, Kamchatka, Moscow, Ivanovo, et al [4]. TBE cases have appeared in new areas of Europe: in the south of Sweden, Denmark and France, [5-9]. Coupled with the increase in the incidence of TBE, there has also been an inclination towards an increase in the severity of the disease, with a rising proportion of meningeal and focal forms [10]. Alertness is caused by the emergence of new forms of TBE, especially those with hemorrhagic syndrome [11].

Molecular typing of the TBEV using different methods (ELISA, molecular hybridization with radioactive oligonucleotide probes and RT-PCR with subsequent sequencing of mainly E gene but recently other gene fragments and even complete genomes) reveals 3 main

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subtypes: Far Eastern, Siberian and European [12-15].

According to the International Committee for Taxonomy of Viruses, TBEV is classified as one species with three subtypes, namely the Far Eastern subtype (mainly isolates from far-eastern Russia, China and Japan), currently widely spread Siberian subtype (earlier isolates from Eastern and Western Siberia, Urals and far-eastern Russia and at present dominant subtype in many TBE endemic regions of Russia and surrounding countries, gradually replacing 2 other TBEV subtype [16] and the European subtype (which comprises almost all known isolates from Europe) [1, 17, 18]. The three TBE virus subtypes are associated with varying degrees of disease severity. Human infections with Far Eastern subtype viruses are usually severe, frequently with encephalitic symptoms (focal meningoencephalitis or polyencephalitis), with an associated fatality rate between 5 and 35% (earlier 20-60%). This type does not cause chronic disease. In contrast, TBE virus infections of the Siberian subtype cause a less severe disease (fatality rate between 1 and 3% (earlier 6-8%)), with a tendency for patients to develop chronic or extremely prolonged infections accompanied by diverse neurological and/or neuropsychiatric symptoms. In contrast to these two forms, infections caused by European strains typically take a biphasic course: the first (viraemic) phase presents as an influenza-like illness lasting 1–8 days with fever, malaise, headache, myalgia, gastrointestinal symptoms, leukocytopenia, thrombocytopenia and elevated liver enzymes, often followed by a symptom-free interval of about 1–33 days and the second phase in 20–30% of infected patients with clinical features of different severity (meningitis, meningoencephalitis, meningoencephalomyelitis or meningoencephaloradiculitis), the appearance of specific antibodies in the serum and cerebrospinal fluid and the fatality rate less than 2% [1, 17, 18].

Recently, a new classification of the tick-borne flaviviruses based on phylogenetic analysis of complete coding sequences of their genomes had been proposed [3]. According to the recommendation the tick-borne flaviviruses should be divided into 4 types (i.e. Western tick-borne encephalitis virus, Eastern tick-borne encephalitis virus, Turkish sheep tick-borne encephalitis virus and looping ill tick-borne encephalitis virus)[3]. However, it has not yet been accepted by the International Committee on Taxonomy of Viruses (ICTV).

Moreover, new phylogenetically distant variants of the TBEV isolated in Irkutsk endemic region, Eastern Siberia, Russia and Mongolia do not evidently belong to any known genetic subtype [19] (GenBank accession numbers EF469662 and EF469661 for strains 886-84 and 178-79, respectively).

Currently, there are 7 formaldehyde-inactivated vaccines against TBE including Moscow Enterprise Institute of Poliomyelitis and Viral Encephalitis and "Entsevir" produced by "Microgen" in Tomsk, based on the Far Eastern strains of "Sofjin" and "205", respectively [20, 21]; FSME-Immun Inject 0.5 ml" and "FSME-Immun 0,25 ml Junior ("Baxter", Austria); "Encepur Adult and Children" (Novartis), based on the Central European strains (Neudoerfl and K23, respectively) [22-24] as well as last but not least vaccine of Changchun Institute of Biological products (ChangChun, China), based on TBEV Far Eastern strain Senzhang isolated in 1953. Additionally, 2 new Russian vaccines based on TBEV Far Eastern strain Sofjin had been approved by Russian authorities in 2010.

Unfortunately, all available vaccine strains belonging to the Far Eastern and European subtypes and isolated 35-75 years ago do not coincide with dominating Siberian TBEV in majority of endemic regions in Russia and nearest countries today. The level of divergence between the genomes of the different strains is known to be more than 20% [25]. To our knowlwdge the presence of neutralizing antibodies in human sera after immunization with European vaccines had been described [1] but cross-protection between available vaccine strains and recent isolates of Siberian subtype remains unclear. Incidence of recurrence in patients who have had a symptomatic TBE form of the disease has been observed, with the development of humoral immunity post-infection [26].

Immediately after the TBEV infection the virus-specific antibodies levels have been observed to increase in both sera and cerebrospinal fluid (CSF): maximal IgM levels were revealed at the early disese stage and later on up to 6 weeks, whereas peak IgG – in late convalescent sera (around 6 weeks). However, IgM antibodies can persist for a few months after infection, whereas IgG – for a lifetime. In CSF, mononuclear cells are predominantly composed of $CD4^+$ T lymphocytes and less numerous $CD8^+$ T lymphocytes, with limited natural killer cells and B-lymphocytes [1].

With a tropism for lymphoid tissue, the TBE virus significantly affects the immune system. Lowered immune deficiency adversely affects the course of the viral infection, causing its severity, tendency to persistance and resistance to therapy. Depth of virus-induced immunosuppression correlates with the severity of the clinical course of TBE [27]. TBEV persistent infection of spleen and lymph nodes had been shown for monkeys and Syrian hamsters [28]. In cases of acute TBE, the decrease in the relative and absolute number of T-lymphocytes in the blood [29] was found. Active proliferation of B cells and a two-fold increase in their concentration in the peripheral blood, with the normalization toward the end of the third month was observed. Research has shown selective loss of T-cell immunity in acute TBE, linked to the multiplication of the virus in the thymus. Depth of virus-induced depression of T-immunity and its duration directly correlate with the severity of the clinical course of acute TBE. In patients with the meningeal form of TBE, secondary immunodeficiency was detected with a primary decrease in the number of $CD3^+$ and $CD4^+$ cells [30]. The antibodies against the TBEV antigen E reflect the active functioning of the B-cell population during the acute infection stage. On the fourth day of the illness, IgM antibodies to TBEV were observed [31, 32].

Immune response after TBEV infection and vaccination is mediated by cytokines. Interferon (IFN) was found to play an important role in controlling the replication of the flaviviruses [33]. Dendritic cells (DCs), which are the main producers of IFN, were the first to be infected with TBEV. Thus, the interaction of DCs, IFN and the TBEV affects the outcome of the infection. Early IFN responses to DCs are modulated not only by the virus, but also by the tick vector and the immunomodulatory tick salivary proteins produced during the virus inoculation into the skin [34]. TBEV infection has been shown to lead to the induction of humoral immune responses against the

structural and nonstructural proteins of the virus [35]. In the cerebrospinal fluid and serum, marked differences are seen in the spectra of the antibodies to viral proteins. The intensity and development patterns of the humoral immune response in TBE are closely associated with a set of allelic variants of the HLA genes. Regularities in the development of antiviral immunity in TBE are non-random in nature [36]. They are largely predetermined by the individual characteristics of the immune system that are closely associated with the HLA genes, namely, IFN-α and IFN-γ. Cell-mediated immunity is highly significant in protecting the body at an early stage of infection. T-deficit and long-term circulation of the IgM class of antibodies indicate a disruption in the effectors of cellular immunity, and are prognostically significant for the development of infection. The results of the genetic studies of TBE patients [37] suggest that the deletion in the CCR5 chemokine receptor gene is a genetic factor associated with severe forms of TBE. Thus, the impaired immune response might be an important factor in determining the pathogenesis of flaviviruses.

Recently, the TBEV NS5 protein has been shown to act as interferon antagonist inhibiting the expression of antiviral genes.

Currently available data on the role of cytokines and chemokines in the TBEV-induced pathogenesis is rather limited. In sera and CSF of patients with TBE elevated levels of inflammation cytokines such as tumor necrosis factor a (TNF-a), interleukin (IL) 1a and IL-6 were detected. During the first week of disease, the levels of those 3 cytokines gradually declined and an inhibitor of cytokine production Il-10 amount increased [38].

A study of the cytokine synthesis in the acute infection of Japanese encephalitis in an animal model (rats and mice) showed an increase in the expression of the proinflammatory cytokines (IL-1β, TNF-α, IL-6) and the chemokine MCP-1-associated with antivirus, particularly, the IFN-response. At the same time, the immunized mice showed an increased production of Th2 cytokines IL-4, and IL-10 suppressed the INF-γ expression. The IL-10 was noted to be an important factor in determining the clinical outcome in Japanese encephalitis virus infection [39, 40].

Our research was aimed at the changes in the regulatory cytokine network in infections caused by infection of permissive tissue culture of human larynx cells (strain Aina 1448 (GenBank (http:// www.ncbi.nlm.nih.gov) accession number AF091006) of Siberian subtype and strain 886/84 (GenBank accession number EF469662) of new subtype [41]. Analysis of the gene expression dynamics of Il-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-18, TNF-α, IFN-α, IFN-γ) after infection with 2 strains of TBEV cells revealed differences.

During the early stage of infection caused by the TBE virus, Aina 1448, activation of the gene expression TNF-γ, IL-6 and IL-18 was observed at 24 hours after infection compared to the absence of mRNA transcription in the control uninfected HEp-2 cells, By contrast, complete inhibition of expression was shown for the genes of IL-4 and IL-8 Consequently, at the early stages of the infection, the TBEV activates the transcription of IFN-γ, causing Th-1 immune response, as well as of IL-18 involved in the synthesis of IFN-γ.

At early stages of an infection both early cytokine IL-6 gene expression activation with subsequent stimulation of antibody-producing cells and immunoglobulin production as well as IL-4 gene expression total inhibition which is known to be Th-1 immune response antagonist.

One might suggest that an imbalance of cytokines is responsible for the development of the prevalent humoral immune response. Because of the infection by the Aina/1448 TBEV, activation of the transcription of IFN-γ was noted in 5 days post infection; the latest seven days of infection, transcription IFN-γ was not detected. In this case, mRNA IL-4 was detected seven days after infection.

Analysis of the mRNA synthesis of 11 cytokines in the later stages of infection (i.e. at days 2, 4, 5 and 7 post infection, with strain 886/84 TBEV) revealed the following data. Two days after the cells were infected with the HEp-2 strain 886/84, the genes of all the 11 investigated cytokines were expressed. After days 4, 5 and 7 of infection no sign of mRNA IL-6 was noted, indicating continued functional activity of this cytokine in the early stages of infection. On day 5, post infection, activation of the gene expression of IL-4 was detected. Obviously, in the early stages of TBEV infection the transcription of cytokines was activated, causing a type of immune response in the body, in the Th-1 cell. A complete inhibition of transcription of IL-4 was also found, which plays a key role in the development of humoral immunity and is an antagonist of the immune response to the Th-1 path. Only in the later stages of infection the IL-4 gene expression was activated that could indicate the inclusion of humoral immunity after the cell immunity. Interestingly, only when infected, cell strain 886/84 revealed the expression of all the 11 cytokines, two days post infection. This phenomenon was not detected with the other strains. We studied TBE patients characterized by the activation of the transcription of IFN-α, IL-12 and IL-18, involved in the synthesis of IFN-γ, but suppressing the gene expression, IFN-γ [42]. Active transcription of IL-6 was noted, with IL-1β gene expression, and suppression of IL-4 and IFN III type (IFN-λ1). At the same time, mRNA IFN-β, IFN-λ2, IFN-λ3, IL-2, IL-10, TNF-α were equally determined or not determined in patients Obviously, during the first 14 days of observation, an imbalance in the Th1 functions and Treg-lymphocyte suppression of the functional activity of Th2, as well as activation of the functions of Th17, B-lymphocytes, macrophages and monocytes was noted in the TBE patients. In the early stage of infection, the activation of the gene expression of IL-6, which helps to regulate the maturation of the antibody-producing cells of B-lymphocytes, as well as the production of immunoglobulin and T cell differentiation into Th-17, was noted to occur, with a complete inhibition of the gene expression of IL-4. Significantly, IL-4 is known to play a key role in the development of humoral immunity and is an antagonist of the immune response to Th-1 path, as shown in the experiments, in vitro.

The study of the gene expression of IFN I, II and III types in the same patients revealed the following data: on day 14 of the illness, with the active gene expression of the IFN-α, IFN-β and IFN-γ gene, the IFN-λ3 was expressed, but the IFN-λ1 and IFN -λ2 were not. At the same time, the suppression of the transcription only of IFN-γ was noted, but not that of IFN-α and IFN-β; transcription IFN III type (IFN-λ1, IFN-λ2 and IFN-λ3) alone was suppressed. On suppression of the gene expression of IFN-

α and / or IFN-β, with the active transcription of IFN-γ, the gene expressions of IFN-λ1 and IFN-λ2 were activated, but not that of IFN-λ3. The data indicate a cyclic pattern of the synthesis of the different types of interferons, which results in the development of an antiviral response. Studies have shown that during the first period of TBE infection, in patients with suppression of synthesis occurred at the transcriptional level, cytokines involved in the anti-virus response, with subsequent activation of the mechanisms of its development. It was noted that during the inhibition of the transcription of the Th1-cytokines that lead to antiviral immunity (IFN-γ, IL-2) genes of type I interferons (IFN-α, IFN-β) were expressed. In suppressing the gene expression of type I interferons, the transcription of IFN-γ, IL-2 and interferon type III were activated. Thus, it has been shown that TBEV has a very negative effect on the patients' immune system, which may be regulated by the immunomodulatory cytokines. Russian scientists described new approaches to TBE therapy [43], aimed at stimulating the self-regulation mechanisms and protection. This applies primarily to the biologically active substances or the cytokines (IFN-α, IFN-γ, IL-1, IL-2, IL-4, IL-6, IL-10, IL-12, TNF, etc.). Implementation of the effects of the cytokines administered was only possible if the activities of all the components of the cytokine network and system security were coordinated. In such a favorable situation in vivo small amounts of endogenous interferon are sufficient. These results suggest the immunomodulatory nature of the proposed therapy, specifically the normalization of the Th-1 and cytokine level of responses.

Thus, the immune system plays a key role in protection against TBEV. The study of the cytokine responses warrants an adequate selection of immunotherapy that enhances the effectiveness of treatment and reduces the risk of complications of the disease. Features of the immune response in TBE involve a number of gene expressions of the cytokines in cell cultures infected with TBEV and should be taken into consideration for vaccine development.

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