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Etiology, clinical manifestations, treatment and prevention of tick-borne encephalitis

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At present, tick-borne encephalitis is registered in Siberia, Far East, Urals, Belarus and central regions of Russia. The viral infection has also been recently revealed among the population of the previously problem free regions: Penza, Yaroslavl, Magadan, Kamchatka, Moscow and Ivanovo. The disease manifests itself in various forms: febrile, meningeal, meningoencephalitic etc. The disease prognosis is favorable in case of a meningeal or febrile form, but significantly worse in case of a meningoencephalitic form – fatal outcomes take place in 25-30% of cases. Residuals in the form of convulsive hyperkinetic syndrome may remain in some patients even if the treatment started in time. Active immunization is the primary tick-borne encephalitis prevention.

Keywords: *tick-borne encephalitis virus, Ixodidae, neuroinfection, tick bites, vaccinal prevention, vaccines against tick-borne encephalitis*

Infection's causative agent and its natural carriers

Tick-borne encephalitis or, according to the International Classification of Diseases ICD-10, spring-summer encephalitis (Russian) is a viral infection affecting arachnoid membrane, gray and white substance and other regions of brain and spinal marrow, spinal nerve roots and peripheral nerves; leads to the development of pareses and paralyses. Feral herd infection of tick-borne encephalitis is etiologically connected with tick-borne encephalitis virus (TBEV), family *Flaviviridae*, ecologically related to arboviruses carried by arthropoda [1, 2]. Like virions of all flaviviruses, TBEV has spherical form up to 50-60nm covered by glycoprotein membrane. Besides humans, TBEV is also highly pathogenic to monkeys and white mice. Piglets and sheep are susceptible to tick-borne encephalitis infection out of domestic animals. Goats and cows may also be infected with TBEV, but the infection often amounts to nothing more than brief viremia and the virus penetrating the animals' milk [1, 3]. Entries of infection in case of tick-borne or alimentary infection are skin and hypodermic tissue or human digestive tract's epithelial cells, from where the virus spreads by blood, lymphatic and/or neural channels, infects blood cells, immune system's organs and other viscera and reaches brain which serves as a place of continuous reproduction of virus and the primary center of pathological neuroinfection's nidus localization [4]. Clinically, tick-borne encephalitis, as a rule, develops in an acute cyclic form with recovery; however, it may with the lapse of time transform into a chronic infection. Infection's development in a primary-chronic form is not ruled out. Acute infection's severe complications may often end with paralysis and fatal outcome. Tick-borne encephalitis's chronic infection with cerebral affections is years-long or life-long [5, 6].

The main virus's natural reservoir is its main carriers – Ixodidae. Congenital infection of ticks maintains the fixed level of the contagious insects. An additional virus's natural reservoir is hosts of the infected ticks: multiple rodents (field mice, chipmunks, hares etc.), other wild and domestic animals, birds. In nature, the virus is maintained by constant circulation within a closed circuit: tick – animals-hosts –

tick. Human infection is a biological dead end for TBEV, as the virus is not further transmitted to other organisms and goes out of natural circulation [5].

Tick-borne encephalitis is characterized by strictly spring-summer seasonality of the disease onset; it is connected with the activity of carriers; sometimes the increase in biological activity is noted twice a year: in spring (May-June) and in the end of summer (August-September) [7]. Human TBEV infection occurs when contagious ticks suck blood. She-tick sucks blood for many days and increases in weight 80-120-fold when totally satiated. He-ticks usually suck for several hours and it sometimes goes unnoticed [5].

Transfer of tick-borne encephalitis virus may occur in the first minutes of highly contagious tick biting into a human. Unless the “cementing plug” containing tick’s saliva virus does not remain in a human’s skin after the insect was removed, infection may still have been transferred. One highly contagious tick may contain an excessive dose of the infection’s causative agents – up to 1,000 viral particles; 0.000001^{th} part of viral pool in human blood may be enough to develop infection [7, 8]. The average number of ticks per 1km of foot track in many nidi of Far East and Siberia is 50-70, given the individual infection rate of ticks in natural (wild) nidi – 2-15%. The virus’s infection rate in ticks in other regions reaches even higher figures: 24.5% - in Perm, 34.7% - in Kirov and 57.8% - in Novosibirsk Regions [8, 9]. Tick-borne encephalitis infection has recently started to be diagnosed among population of the previously safe regions: Penza, Yaroslavl, Magadan, Kamchatka and other regions. Tick-borne encephalitis infection cases are also registered in Moscow and Ivanovo Regions [10].

Interestingly, the disease in Europe and Siberia takes a milder form than in the eastern areal, especially in Far East. It gave ground to differentiate between western and eastern tick-borne encephalitis types and their causative agents, accordingly. Infection’s causative agent belongs to one and the same kind of tick-borne encephalitis virus everywhere; however, virus’s tick pool in each territory consists of a mixture of strains, different genetically and serologically. TBEV strains vary in virulence, although convincing data on the correlation of virulence

with virus's antigenic qualities have only recently been presented [3]. It is also known that tick-born encephalitis lethality in the European part of Russia is 1-3%, while in Far East fatal outcomes occur in 12-25% of cases [5, 11].

Human tick-borne encephalitis infection occurs not only after the tick bite. An alimentary infection is also observed: e.g., when drinking raw milk containing virus of infected goats and cows. However, the share of this type of infection in comparison with the transmissible TBEV-infection transfer is insignificant [1, 5].

Clinical manifestations of tick-borne encephalitis and its consequences

Incubation period at the primary TBEV infection is 8-23 days (usually – 10-12 days). Prodromes are sometimes observed: weakness, malaise, headache, nausea, sleep disorders. Transitory weakness in limbs and neck muscles, facial and cervical skin numbness are noted. Clinical manifestations of tick-borne encephalitis and its course are various. The acute tick-borne encephalitis takes a toxicoinfectious course from the first days of disease. Symptomatology is formed by the 3 main syndromes: general infectious, meningeal and focal affection of nervous system. The disease often has an acute onset: chill and body temperature increase up to 38-40^{o}C. Fever continues for 2-10 days. Common ailment, sharp headache, nausea and emesis, fatigue, fatigability and sleep disorders appear. Hyperemia of facial, cervical and pectoral skin and of oropharyngeal mucous tunic and ocular and conjunctival injection are noted in acute period. Panalgia and melalgia occur. Muscular pains, especially severe in muscle groups, where pareses and paralyses occur later, are typical. Sometimes they are preceded by numbness, paresthesiae and other unpleasant sensations. Stupefaction and obnubilation may develop in the onset; their aggravation may lead to coma. However, the disease usually takes a mild, obliterated course with a short fever period. Tick-borne encephalitis's acute period continues for 6-8 days in typical cases; sometimes – for 3-14 days. Different-sized erythemae often appear in the ticks' biting sites. The so called migrating annular erythema is a clinical marker of a different infection – tick borne borreoliosis, or Lyme disease, also carried by ticks [12].

Despite the variety of manifestations of the acute tick-borne encephalitis's period, a cardinal disease's syndrome may be singled out in each case. Given that, scientists distinguish between 3 main clinical forms of the disease: fever, meningeal and focal meningoencephalitic. Less widespread poliomyelitic and polyradiculoneurotic forms are diagnosed less often [13-15].

Fever form of the disease is characterized by favorable course and fast recovery. Fever duration is 3-5 days. Primary clinical signs are toxicoinfectious manifestations: headache, weakness, nausea with obliterated neurological symptomatology. Liquor parameters are normal.

Meningeal form is the most widespread form of tick-borne encephalitis. Patients complain of severe headache intensifying at the slightest head motion, vertigo, nausea, one-time or repeated emesis, ophtalmalgia and photophobia. Patients are flaccid and deferred. Rigidity of occipital muscles, Kernig's Brudzinski's symptoms are detected. Meningeal symptoms remain throughout the fever period. Sometimes they also manifest themselves at normal temperature. Moderate increase in the number of lymphocytes and protein concentration increase in liquor. Increased intracranial pressure. Cerebrospinal fluid alterations that have appeared in the acute period of disease may remain for a long time, even in the recovery period. Fever duration is 7-14 days. Outcome is always favorable.

Meningoencephalitic focal form of tick-borne encephalitis takes a severe course and is characterized by high lethality. Patients are flaccid, deferred, sleepy and complain of severe headache, nausea and emesis. Rigidity of occipital muscles, Kernig's Brudzinski's symptoms are manifested. Delirium, hallucinations, psychomotor excitation and loss of orientation in space and time are often observed. Epileptiform fits may occur. Hemipareses, subcortical hyperkinesiae, stem disorders and focal affections of cerebral nerves (pairs III, IV, V and VI; slightly more often – pairs VII, IX, X, XI and XII) are typical of meningoencephalitic forms [16]. Lymphocytosis and increased protein concentration are noted in cerebrospinal fluid in the acute period. Recovery period

after the acute focal tick-borne encephalitis is long-term, up to 2 years. The developed atrophic myoparalyses recover only partly.

Two-wave tick-borne encephalitis is a clinically special variant of how an acute infection may develop. The disease has an acute onset: chill, headache, nausea, emesis, vertigo, melalgia, sleep disorder, anorexia and characteristic two-wave fever. The first two-wave fever lasts for 3-7 days and is mild. Obliterated meningeal symptoms and no affection of cerebral nerves are noted. No significant liquor alterations. Vegetative disorders are noted in the setting of intoxication. The period of apyrexia comes after the first wave; it lasts for 7-14 days. The second fever wave starts as acutely as the first one; body temperature rises highly. Patients are flaccid, deferred, have nausea, emesis, mild meningeal and focal symptoms of the central nervous system's affection. This is a qualitatively new stage of the disease; it always takes a severer and longer course than the first one [12, 14].

Subclinical, or obliterated, form of tick-borne encephalitis appears in the vast majority of primarily infected patients. In Primorye, tick-borne encephalitis infection with no clinical manifestations in the form of continuous TBEV antigenemia in leukocytes and peripheral blood is revealed in 1 out of the 4 tick-bitten [7]. This is the main way of immunity formation in native local population of endemic territories. Sometimes the infection forms that had not been revealed on time may result in the long-term virus infection carrier state and serve as a reason for the so called primary-progredient (later – primary-chronic tick-borne encephalitis infection) to develop. Perception of chronic tick-borne encephalitis is based on the long-term TBEV persistence in people suffering from this infection's obvious symptoms for years, decades or life. As a rule, these patients have hyperkinetic syndrome, Kojewnikoff's epilepsy, amyotrophic lateral sclerosis, epidemic encephalitis, meningocephalitis, syringomyelia, progressive polioencephalomyelitis etc. TBEV persistence may be determined by immune-enzyme analysis (IEA). The most reliable way of revealing chronic tick-borne encephalitis infection is the analysis of viral RNA in the patient's blood and tissue samples examined by polymerase chain reaction. According to clinical data, the

frequency of transformation into a chronic infection is 3-11% of the total number of acute tick-borne encephalitis cases [6, 8, 17].

Recovery after acute tick-borne encephalitis depends on the form of infection's manifestation and its severity [5].

N.V. Morgatskiy has described peculiarities of tick-borne encephalitis course in children in detail. He has shown that tick-borne encephalitis in them mainly takes a fever (60.5%) and meningeal form (22%), rarer – a focal form (14.1%); meningoencephalitic disease form makes up to 79.3% in the structure of the latter. Tick-borne encephalitis in small children is characterized by shorter duration and smaller intensity of general infectious and cerebral manifestations, while in schoolchildren and adolescents it is characterized by the prevalence of meningeal and focal manifestations and disease's chronization in 4.9% of cases [18].

Immunity and cytopathic mechanisms of the infection

Relative and absolute amount of T lymphocytes in blood is reduced at acute tick-borne encephalitis. Deficiency of T cells is revealed in the first days of disease and remains throughout the first 2 weeks. Function of B lymphocytes is not disturbed at the acute infection; active proliferation of B cells and their doubling in peripheral blood with normalization by the end of the 3rd month are also noted. The researchers associate the T-immune system's selective affection with virus replication in thymus. Majority of the virus-induced depression of T-immunity and its duration are in direct correlation with the severity acute tick-borne encephalitis's clinical course [5].

M antibodies (immunoglobulins, Ig) to TBEV are revealed on the 4th day of disease; synthesis of early IgM switches to antiviral G antibodies approximately on the 21st day with the subsequent increase in titer of the latter. IgM level remains high for 3 months and then decreases; however, these antibodies may be revealed even as far as 3 years later in patients with chronic infection. IgG antibodies usually remain for decades in patients who have recovered from an acute infection [19].

Diagnostics of tick-borne encephalitis

Clinical detection of tick-borne encephalitis on the first stage is based on the known clinical-epidemiological data. Infection cause may be determined in most observations: trip to the forest, tick bite, drinking raw infected milk. Probable duration of incubation period is estimated at once; clinical studies may reveal neuroinfectious character of the disease. Provisional diagnosis must be confirmed by a laboratory analysis [12]. In practice, diagnosis “tick-borne encephalitis” is, as a rule, established by IEA in case of a fourfold increase in the titer of virus specific antibodies in paired sera. Repeated examination may be conducted 7-10 days later. Antibodies in high titers are usually revealed on the 10^{th}-14^{th} day of disease, sometimes even earlier, and reach high level by the end of the month. Even a one-time observation of high virus specific IgM concentration should be considered reliable evidence in favor of the clinical diagnosis “tick-borne encephalitis”. Viral RNA revealed in serum and liquor samples at tick-borne encephalitis may serve for diagnosing seronegative form of tick-borne encephalitis, lingering recovery, prognosticating the second wave of tick-borne encephalitis fever and the possibility of the process’s chronization [20, 21].

TBEV RNA PCR-analysis and IEA are used to indicate viral antigen in ticks removed from people. Urgent seroprophylaxis of the bitten by intravenously administering specific anti-encephalitic human immunoglobulin is recommended in case the tests are positive [4, 8, 22].

Differential diagnostics

It is important to take into account the possibility of a patient’s developing Japanese encephalitis, epidemic hemorrhagic fever, enterovirus meningitis, tick-borne rickettsiosis, Lyme disease (borreoliosis) etc. [5, 23].

Means of specific prevention and treatment of tick-borne encephalitis

Non-specific method of the infection’s prevention by exterminating virus carriers in nature was proposed as far back as in 1937-1938. It was proposed to treat forest blocks with lysol, naphthalene and phenol solutions. DDT (dichlorodiphenyltrichloroethane) and HCCH (hexachlorocyclohexane) had later

been widely used as long-term acaricides by ground and air spraying. However, their intolerable harmfulness and danger for the environment and human health was soon proved [24].

Other effective means of non-specific prevention of tick-borne encephalitis are community health education and personal and collective protection measures against ticks attacking and biting.

Specific antiviral vaccinal and seroprophylaxis of tick-borne encephalitis is considered undoubtedly the most effective and prospective anti-encephalitic protection. At present the vaccination using the available drugs covers only a very limited contingent of population, while the tick-borne encephalitis's infection in the Russian Federation continues increasing. Urgent seroprophylaxis using specific immunoglobulins against tick-borne encephalitis for people bitten by contagious ticks remains quite relevant in these conditions. It has been shown that passive immunization by antiviral antigens of people before or just after the infected tick's bite sharply reduces the tick-borne encephalitis's infection and especially reduces the risk of severe neuroinfection. Protective effect is achieved by administering specific immunoglobulins as soon as possible – within 2-3 days after tick's bite. The need in urgent seroprophylaxis is determined by virus laboratory analysis of the tick that has bitten a human [16, 22]. The increasing tick-borne encephalitis's infection, frequent cases of the severe disease's course and fatal outcomes and continuous increase in the number of people disabled with the unhealed tick-borne encephalitis in Russia means that the tick-borne encephalitis's prevention in our country is not conducted to the full extent despite the availability of vaccinal drugs.

Vaccination against tick-borne encephalitis

Vaccination against tick-borne encephalitis in the Russian Federation is conducted according to the epidemiological indications (Order #51n of 31 January 2011). Immunization is to be conducted among population living in territories enzootic for tick-borne viral encephalitis and also people who have come to these territories to conduct the following works: agriculture, hydrotechnology, construction, earth excavation and handling, procurement, fishing, geology,

exploration, expedition, disinfestation and fumigation; logging, wood clearing and development of wood and recreational zones; people who work with living cultures of the tick-borne encephalitis's causative agent; people visiting territories enzootic for tick-borne encephalitis for recreation, tourism, work in personal holdings and garden plots. Cohort immunization of schoolchildren is conducted in a range of regions or Russia. Effective protection is expected within 3 weeks after the administration of the first vaccinal dose. 4 vaccines against tick-borne encephalitis are registered and used in Russia. All vaccines are inactivated, aluminum-hydroxide-adsorbed, differ in virus strains, antigen and protein concentration. They are stored at 2-8^{o}C [25].

Tissue culture purified concentrated inactivated dry **vaccine against tick-borne encephalitis** (Russia, Moscow). Contains TBEV antigen – Sofin strain. Does not contain preservatives, antibiotics and formaldehyde. Protein – up to 30mcg. Solvent – ammonium hydroxide. Is used in people over 3 years of age. Course: 2 doses 5-7 months apart (at least 2 months). The first revaccination is in 1 year, then – every 3 years. The vaccine is administered subcutaneously (s/c) in infrascapular region or intramuscularly (i/m) in deltoid muscle.

EnceVir – tissue culture purified concentrated inactivated liquid vaccine (Russia, Tomsk). Contains virus meal (TBE virus strain #205, growth on the chick-embryo cell culture). 1 dose (0.5ml) contains up to 0.5mcg of chick protein, up to 250mcg of human albumin and 0.3-0.5mg of aluminum hydroxide. Does not contain antibiotics and preservatives. Is used in people over 3 years of age. Course: 2 doses 5-7 or 1-2 (emergency scheme) months apart. The first revaccination is in 1 year, the subsequent – every 3 years. The vaccine is administered i/m in deltoid muscle.

FSME-IMMUN, FSME IMMUN Junior (Baxter Vaccines AG, Austria). 1 dose (0.5ml) for children contains 2.38mcg of Neudoerfl virus strain (growth on the chick-embryo cell culture), phosphate buffer, human albumin. Does not contain preservatives, antibiotics and heterogeneous proteins. Scheme: 2 doses 1-3 months apart, the first revaccination is in 5-12 months, then – every 3 years. Emergency

scheme: 0-7th-21st day – 9-12 months. Children's dose – Junior (6 months to 16 years) – 0.25ml. Children of 0-1 years of age are vaccinated in case of a high infection risk.

Encepur Adults, Encepur Children (Novartis Vaccines and Diagnostics GmbH & Co. KG, Germany). 0.5ml (for patients over 12 years of age) contains 1.5mcg of K23 virus strain antigen and aluminum hydroxide (1mg); 0.25ml (for children of 1-11 years of age) – 0.75mcg of K23 virus strain antigen. Does not contain preservatives, protein stabilizers and human blood components. Scheme: 2 injections 1-2 months apart, the first revaccination is in 9-12 months, then – every 3-5 years. Emergency scheme: 0-7th-21st day – 9-12 months [26].

Painfulness, edema, induration (sometimes with lymphadenopathy) and granuloma (rarer) may be noted in injection sites. Short-term body temperature rise, headache, melalgia, nausea and emesis are sometimes observed after the first dose; such a response to the subsequent doses is observed very rarely. Allergic reactions are extremely rare. Contraindications (apart from the general contraindications against vaccines) – hen's egg allergy. The vaccine may be administered 2 weeks after labor. Use of FSME-Immun is not contraindicated during pregnancy and breast feeding. Contraindications for the Russian vaccines are also tuberculosis, rheumatism, hereditary and degenerative diseases of central nervous system [25].

A lot of publications worldwide are dedicated to immunogenicity and efficacy of vaccination against TBE. According to Russian scientists, all vaccines against TBE used at present in the territory of the Russian Federation produce high levels of G antibodies after the immunization course has been completed (from 82.9±6.4% for the Russian dry vaccine to 90.9±9.1% for the German vaccine) and the protective level of antibodies remains for a long-term observation period (7 years) [27, 28]. The best positive example of epidemiological efficacy is the vaccinal prevention experience against TBE in Austria, where cohort immunization has been conducted since 1981. By 2001 the immunization coverage had reached 86% and exceeded 90% in the certain highly endemic regions. Tenfold reduction in

the TBE morbidity rate had been achieved in this setting; since 2001, sporadic cases of TBE infection have been observed only among the non-immunized people [29].

Human immunoglobulin against tick-borne encephalitis (Ig) is administered i/m once (dose – 0.1ml/kg) to the non-immunized people 96 hours before visiting nidi. The protection starts in 24 hours and lasts for ca. 4 weeks, then the dose is repeated. Ig is also administered to the non-immunized people within 96 hours after the tick's bite – 0.1-0.2ml/kg (slowly, deep inside the muscle) by 5ml in different body parts. The drug is not administered after day 4. Interval between the specific immunoglobulin administration and vaccination against tick-borne encephalitis should be at least 4 weeks. Pruritus, pains and anaphylactic reactions (very rarely) are possible in the immunoglobulin injection site [25, 26].

At the FSBI "Scientific Center of Children's Health" (vaccinal prevention department), the immunization against tick-borne encephalitis has been conducted since 2007. 2 vaccines against tick-borne encephalitis are used: FSME-IMMUN – for people over 16 years of age and FSME-IMMUN Junior – for children of 1-16 years of age (Austria). 779 people have already been vaccinated (332 adults and 447 children of adolescents younger than 16 years of age). Immunization is primarily conducted in spring. Both vaccines are well-tolerated; complaints of local reactions in the form of mild painfulness in the injection site in the first 1-2 days after the self-made injection are rare among the patients. No case of severe or systemic reaction to the administration of either vaccine has yet been registered.

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