TRANSLATION NO. 512

DATE: July 1962

DEPARTMENT OF THE ARMY
Fort Detrick
Frederick, Maryland

Sov. Med. 20(1) P. 3-7 '56

Translated from: Journal unknown
Translator: Sfc E.N. Ewing, Tech. Lib.
Tech. Info. Div. CBL, Ft. Detrick, Md.

Misc Tr. 572

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New Developments in the Epidemiology, Prophylaxis and Diagnosis of Tick-Borne Spring-Summer Encephalitis.

Ye. N. Levkovich and Ye. S. Sarmanova

The problem of tick-borne encephalitis is of importance in many Rayons and Oblasts of the Soviet Union.

An analysis of the occurrence rate during recent years in the different regions of the Soviet Union and abroad (Czechoslovakia, Austria, Bulgaria, Germany) shows an increase in the number of cases of tick-borne encephalitis. Also, our knowledge about the territorial distribution of tick-borne encephalitis has been significantly broadened. Epidemic outbreaks of this disease have been noted in the Far East, in Eastern and Western Siberia, in Kazakhstan, in the Ural Mountains, in the Ural, in Krasnoyarsk and Altay Krays, in Leningrad Oblast, and others. The geographic location of these outbreaks is fovorable for the existence of the disease's vectors - ticks of the Ixodidae family. The vigorous development of industry and construction in many of the oblasts has brought in its wake a relocation of masses of the population into previously uninhabited forest regions for the construction of new cities, settlements, mines, railroads and other objects. The intensive prospecting that is being carried out in these places, with a lack of appropriate prophylactic measures, has contributed to an appearance of new natural foci of tick-borne encephalitis and to an increase in the disease rate.

A diffuse, often sporadic pattern of the disease rate, afflicting simultaneously a large member of inhabitated points, is characteristic. A typical example of this would be Kemorovo Oblast, where massive outbreaks of this disease have been noted since 1952. In 1952, cases of tick-borne encephalitis were registered in 199 populated areas; in 1953 it once again appeared in 344 populated areas; in 1954 - 173; and in 1955 - 336 new populated areas. A similar occurrence was ascertained also in Molotov and Sverdlovsk Oblasts, Krasnoyarsk Kray, and others.

An analysis of the causes that contribute to such a vast spread of the tick-borne encephalitis points out the peculiarities of the biocenotic factors which combined in those years to cause the emergence of large quantities of ticks and also contributed to an active propagation of the virus in them (the climate, the presence of hosts for the ticks, their composition, etc.). Our investigations on the virus carrying of the ticks I. persulcatus, conducted in 1953-1955 in Kemorovo Oblast, indicate their high spontaneous infected condition in many of the Oblasts nidi - as high as 40%, which greatly exceeds the figures given in the literature for the infection rate of ticks in the other oblasts of the Soviet Union (A.A. Smorodintsev - in the Far East - 5%; Ye. N. Levkovich, P.A. Petrishcheva - Leningrad Oblast - 0-10%). The close contact with these potentially dangerous nidi, which is being brought about by the increased population, both in their daily life and at work, has rendered them epidemiologically active. In many places this has been contributed to by the inadequacy of the prophylactic measures conducted by the organs of the Public Health Service.

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A characteristic epidemiological peculiarity of tick-borne encephalitis during many recent years is the high disease rate among the urban population (up to 64% in some nidi) and among children in ages from 3 to 16 years (to 90% in Kemorovo Oblast and others). The noted peculiarity is a result of social-domestic factors, which are related to the nearness of the disease's vectors.

The disease rate of tick-borne encephalitis is not always connected with out-of-the-way taiga areas. It can also develop in the so-called well-populated regions with permanent contingents of population. Tick-borne encephalitis may be observed in these regions for a period of many years in the form of isolated sporadic cases and sometimes even in small outbreaks. A significant number of the cases in these regions fall on the indigenous population, with housewives and children prevailing among those stricken (Karatuz Rayon of Krasnoyarsk Kray, Kyzujegeyev Rayon of Kemorovo Oblast, etc.).

Outbreaks of the disease have been noted in the forest-steppe and brush zones (Mariin and Topkin Rayons of Kemorovo Oblast, 1953-1954; Karatuz Rayon of Krasnoyarsk Kray, 1950-1951). According to the findings of M.S. Shotser and M.S. Kavydova, the disease rate in the forest-steppe rayons of Krasnoyarsk Kray comprised 87% of the entire disease rate for tick-borne encephalitis. The numerically predominant species of tick in these rayons proved to be a tick (H.concinna) that provides 77.4% of the collection of all the tick species. Its spontaneous infected condition by the virus has been proved (M.S. Kavydova, N.V. Voshchakina).

In 1954, Ye. N. Levkovich was able to isolate the tick-borne encephalitis virus from Camasoidea collected from rodent nests in endemic areas of tick-borne encephalitis.

The role of these species of ticks in the general circulation of the tick-borne encephalitis virus (TBEV) is not completely clear at the present time, although it is very possible that just they are the carriers of the virus in the populated regions.

The findings that were received indicate that the epidemiological importance of separate species of ticks is dissimilar in different landscape zones. From this emerges the necessity for a careful study of the parasite fauna of the separate nidi and for an investigation for the virus in all species of Ixodes and also Camasoidea.

The heterogeneity of the epidemiological structure of the nidi, even within a single oblast, in regards to the peculiarities of the microclimate and the character of the population's contact with the nidus, forces one to think about the necessity for typing the nidi and a differentiated approach in the conduct of antiepidemic measures in the separate concrete foci of the disease.

The observations on tick-borne encephalitis that have been conducted in the different regions of our country have significantly broadened our understanding of the clinical manifestations of the acute and chronic forms. At present it is considered an established fact that the basic clinical manifestations of tick-borne encephalitis in the different oblasts of the Soviet Union are analogous, but differ by their course and outcome. Of particular note are the various degrees of the

progressive conditions, the various degrees and gravity of the invalidism after recovery from the disease, as well as the large disparity in the percentage of lethality. An analysis of the data on the study of the disease's clinic, particularly in the eastern regions of the country, for a series of recent years, indicates the peculiarities of its course: an increase in the occurrence of abortive forms (sometimes 4-5 times that of the prewar disease rate in Molotovo Oblast); a decrease of encephalytic forms and, particularly, of Moskovnikoff's disease; a large percentage of relapsing forms; a decrease of cases of the progressive course; a decrease in the percentage of lethality. It was also noted that the clinical forms and the course of tick-borne encephalitis vary significantly in different years. There are new variants of the basic forms appearing, which differ from them to such a degree that they are treated as new disease entities.

A special neuroinfection, which is near to tick-borne encephalitis, is being observed in separate regions of our country at the present time (Leningrad and Moscow Oblasts, and the Udmurt ASSR). It has been named the diphasic meningo-encephalitis (A.A. Smorodintsev et al) or milk fever (N.P. Chumakov et al). The pathogen is a neurotropic virus that is difficult to differentiate from the viruses of spring-summer tick-borne encephalitis, louping ill, or Omsk hemorrhagic fever. The main vectors of this disease are the ixodid ticks - I. ricinus; in the rayons of the Udmurt ASSR - I. persulcatus.

Not all of the cases of diphasic meningo-encephalitis are related to a person being bit by a tick. A huge majority (by the data from Leningrad Oblast - as high as 60-90%) of them bear a domestic-group character and are related to the consumption of raw goats' milk, the goats having had contact with the ticks while on pasture. Serological examination of the blood of the goats confirmed their broad contact with the pathogen of meningo-encephalitis. It was established that the clinical picture of the disease in humans was the same with any of the described routes of infection. S.G. Drozdov has received important findings indicating a possible penetration of viruses into the milk in goats infected with the viruses of milk fever, tick-borne encephalitis, louping ill, and Omsk hemorrhagic fever. The possibility of the penetration of the tick-borne encephalitis virus into goats' milk has also been experimentally proved by Ye. N. Levkovich and T. A. Borodina in 1953.

A disease that is analogous to the diphasic meningo-encephalitis by clinical picture was described in 1948-1950 in the regions of Bohemia and Moravia (on the border between Poland and Czechoslovakia). The disease was being transmitted by the tick I. ricinus. A detailed study of this disease's viral strain showed an almost complete identity with the virus of Russian tick-borne encephalitis. According to the opinion of the author, the antigenic differences that they displayed were no more than those encountered between different strains of the same virus. The disease was named the Czechoslovakian tick-borne encephalitis.

According to the findings of A.N. Shapovala, who worked in several regions of Western Siberia during the 1953-1954 season; the most characteristic clinical form of the acute period of tick-borne encephalitis is the meningeal type of illness. The bulbar-paralytic and other forms of the disease are encountered rarely, in comparison, no more than 3-4% of the cases when compared to the total number. The percentages of the chronic course of the disease and of the lethality were also low. A large number of worn-out and abortive forms was noted.

A significant portion of the illnesses took courses along the type of the diphasic meningo-encephalitis. Thus, in Kemerovo-Tudzhensk, in 1953, a relapsing course was noted in 23%, in 1954 - in 12% and in 1955 - in 21.3% of the cases.

The mildness of the disease's clinical course, the frequent relapsing course, the favorable outcome in the huge majority of cases, and the almost complete lack of lethality in the separate foci, point out the great variability of the forms of tick-borne encephalitis and draw them close to the diphasic meningo-encephalitis.

The observations conducted by V.V. Pogodina, in one of the regions most afflicted with tick-borne encephalitis, indicate the possibility of a genesis of domestic illnesses with this form. Her material gives a basis to suspect the alimentary route of infection in 12 patients. In half of the patients the illness took a course along a type of serous meningitis; in 5 it took an abortive course; in one a polioencephalomyelitic - form was observed; in one a meningo-encephalytic form was observed. The diphasic course of the disease was noted in 5 of the patients. All of the patients recovered completely.

Cases of domestic-group illnesses of tick-borne encephalitis, related to the use of raw goats' milk, have also been registered in other oblasts (Molotov, Sverdlovsk).

Without concerning the question about the nosological individuality of the diphasic meningo-encephalitis and the diphasic milk fever, it is necessary to turn our attention to the possibility of an alimentary route of infection (through milk) with tick-borne encephalitis. This possibility may be increased by concurrent animal diseases (pereplasmosis, etc.) that heighten the permeability of the vascular system, by the introduction of new animals into regions endemic with tick-borne encephalitis, and by other causes.

In virtue of the process of evoluntionary mutability, all of the variety of existent and possible etiological forms of viral infections in our vast country has not been completely established and are subject to further investigation.

During recent years, important investigations have been conducted on the cultivation of tick-borne encephalitis virus in malignant tumors of experimental animals (S.G. Zuyagin, 1952; A.I. Ivanenko, 1952 - 1955; A.V. Rshenichnov, et al). At the present time this method (A.I. Ivanenko) is widely used for the preparation of diagnosticums for the complement fixation test and also for specific diagnostic and therapeutic sera. The well known property of the tick-borne encephalitis virus to multiply on chick-embryo tissues is widely used for the preparation of diagnosticums, vaccines and for other purposes. At the present time, in our laboratory, a new preparation of a diagnosticum has been developed from chick-embryo tissues for the complement fixation test. This diagnosticum is prepared from the tissues of the whole embryo. It is very inexpensive and possesses high specificity and sensitivity.

In a study of the mechanism of the virus's circulation in nature in recent years (A.L. Bumina, 1950 - 1955), there was a different ability shown by the tick I. ~~persulcatus~~ to receive the tick-borne encephalitis virus, depending on its feeding on fresh or immune ahimals. With a simultaneous feeding of infected ticks and fresh ticks on an immune animal, infection of the fresh ticks does not occur.

The results of these experiments are particularly well seen on young immune animals. After feeding on an immune animal, the infected tick-donors retain the virus and transmit it to their progeny, although in these cases the viral titer in the next stage was somewhat below that of the infected ticks that were fed on fresh animals. These facts indicate a special role for immune animals in the virus's general circulation in nature. It is very possible that they play the role of a factor that limits the spread of the virus. Together with this, it is also without doubt that the circulation of the virus in the organism of an immune animal, especially in the foci having a high spontaneous infection rate of ticks, cannot help but exert an influence on its properties (for example, a special resistance to neutralizing antibodies is possible), which is indicated by the cases of illnesses among persons living for an extended period in foci of tick-borne encephalitis, whose blood sera contain a high titer of neutralizing antibodies, and which is also indicated by the singular instances of repeat illnesses by this form.

With the purpose of studying the formation of immunity, we investigated blood sera from patients with different forms of tick-borne encephalitis for the presence of neutralizing antibodies. The patients selected for this had different forms of tick-borne encephalitis: a meningeal form, a worn out form, and a form with a diphasic relapsing course by the temperature curve. All of the patients had a short, 2-6 day, incubation period. It is necessary to note that they were city residents and visited the taiga usually a single time, therefore we could accurately establish their incubation period. Blood was taken 2-3 times from each patient, beginning from the 1st. - 3rd. day with intervals of 7 - 10 days. Investigation of the buildup of the virus-neutralizing antibodies, in all of the forms of tick-borne encephalitis that we studied, showed the presence of high neutralizing indices even in the first days of the disease. The neutralization indices in these patients ranged from 110 to 5630 and higher. The quantity of specific antibodies in the meningeal form rapidly grew and increased many times (sometimes to 200 times) in all of the patients by the 10th. - 12th. day of the disease. The same picture was observed in the patients with the worn-out form of the infection. A different one was noted in the patients with the diphasic course of the temperature curve. Often the high antibody titers that were observed in the first days of the disease remained without change by the 10th. - 12th. day of the disease. An increase of antibody titer of 2-3 times was observed in only three of the patients with this form. The active growth of neutralizing antibodies in the diphasic course of the disease was noted later, after the 20th. - 30th. day of the disease. These findings, which indicate a retarded immunological reactivity in some forms of tick-borne encephalitis, cannot be explained by the peculiarities of the microorganism alone and are probably related to properties of the pathogen. Data exist that tell about changes in the skin reactivity during the disease process of tick-borne encephalitis.

In 1954 - 1955 a study was conducted on the possibility of staging an intracutaneous test in order to test its diagnostic importance and to test the possibility of judging the intensity of immunity by the skin test. The test was made with a dry tick formolvaccine prepared from a strain of "Sof'in" which was injected intracutaneously, 0.2 milliliter each. The results were evaluated after 24, 48 and 72 hours by the usual plus system. An analysis of the results indicates a high percentage of positive reactions: in a group of patients after the 18th. - 35th. day of the disease - 65% (11 examinations); in convalescents - 61% (of 24); in those vaccinated and revaccinated against tick-borne encephalitis - 100% (25); and also

in a group of the population of the foci - 53% (15). The control group gave a positive reaction in 12% of the cases (25 people). The possibility of evaluating the intensity of immunity by the skin test can help in the selection of contingents to be inoculated, in retrospective diagnosis, and also for other antiepidemic purposes.

In recent years achievements have been received in the area of serological diagosis of tick-borne encephalitis which insure the advancement of developed methods into practive in the local laboratories, which will significantly broaden the perspective of epidemiological investigations and clinical observations.

These achievements are related to the use of the complement fixation test (Ye. N. Levkovich, A.A. Smorodintsev, V.I. Il'yenko, O. Ye. Rzhakhova). With the help of this test one can diagnose tick-borne encephalitis by the presence of complement-fixing antibodies in the blood sera of patients and convalescents, and also by the presence of the virol antigen in the patients' blood and spinal fluid in the disease's acute period. There are many methods for the preparation of standard antigens for this test at the present time. The most wide-spread and broadly used at the present time, however, are the inactivated antigens prepared from virus-containing tissues of mouse brains, from chick embryos, and from tumor tissues. Should it be necessary to detect the antigen a method of preliminary enrichment of the original material on tumors (A.I. Ivanenko) or embryos (Ye. N. Levkovich and O. Ye. Rzhakhova) is proposed for increasing the reaction's sensitivity. It is possible by these methods to expose minute concentrations of the virus in the original material in a comparatively short time, and also to identify the isolated pathogen.

We must acknowledge, however, that the methods of serum-diagnosis existing at the present time are still complex, protracted and not always applicable (the prodrome period, the first days of the disease). Further efforts toward the development and improvement of serological reactions, the creation of new highly specific antigens and type-specific sera are required. Together with this it is necessary to find quicker diagnostic procedures.

New types of vaccine against tick-borne encephalitis have been created recently: a dry purified concentrated vaccine and embryo vaccines. These preparations showed high immunogenic and antigenic activity under experimental conditions on laboratory animals and volunteers, and also in epidemiological observations in foci of tick-borne encephalitis.

The dry concentrated tick-borne-encephalitis vaccine, prepared by the method developed by Ye. N. Levkovich in 1952, showed high immunogenic properties both in an experimental check on laboratory animals (it protected the animals from a 113,000-LD_{50} dose of the virus with an intraperitoneal injection), and in experiments on volunteers. In 1953 - 1954 the vaccine was used in an epidemiological experiment. There were no illnesses among the persons who were injected with the dry vaccine this season. An active growth of specific neutralizing antibodies (index to 10,000) was detected in the blood sera of those inoculated (142). Even the sera of children, who were injected with a total of 1.5 ml of the dry vaccine, possessed high neutralizing titers. This circumstance allowed us to change to decreased doses of the vaccines used at the present time and with vaccination of the liquid vaccine, and by this to increase the possibility of a greater coverage of the population of the endemic areas by the immunizations.

The active development of methods is also proceeding in the preparation of hyperimmune specific sera, particularly in the preparation of gammaglobulin against the tick-borne encephalitis virus (I.L. Rodin, A.G. Andzhaparidze et al).

In addition to the development of methods for the specific prophylaxis of tick-borne encephalitis, important successes have been achieved in rendering the natural foci harmless through the direct destruction of the ticks in nature with preparations of hexachloro-cyclohexan and DDT (N.N. Gorchakovskaya et al) and also in the conduct of zooprophylaxis (V.N. Popov).

Conclusion. The successes achieved in the study of tick-borne encephalitis are still inadequately used in practice. The quantitative coverage of the population of foci of tick-borne encephalitis, which requires immunization, and the quality of completed immunizations are still not completely satisfactory. The organization and timely conduct of this powerful measure, which has completely justified its use, is necessary. Also required is a broader introduction into practice of the measures aimed at the destruction of the ticks by means of processing the territories of the foci with preparations of DDT and hexachloro-cyclohexan in conjunction with treatment of the cattle with acaracides.

The most important element of disease prevention is the enlargement of the sanitary-educational work among the population. There is no doubt that the disease rate of tick-borne encephalitis can and will be lowered in the near future. There exists a sufficiently practicable arsenal of ways and means for this. It is only necessary that they be properly used.