Vaccine 28 (2010) 2827–2831

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Vaccine failures after active immunisation against tick-borne encephalitis

Charlotta Rydgård Andersson[a,*], Sirkka Vene[b,c], Mona Insulander[d], Lars Lindquist[e], Åke Lundkvist[b,c], Göran Günther[f]

[a] Institution of Medicine, Unit for Infectious Diseases, Karolinska Institutet, Karolinska University Hospital, Solna, Sweden
[b] Swedish Institute for Infectious Disease Control, Solna, Sweden
[c] Karolinska Institutet, Stockholm, Sweden
[d] Department of Communicable Disease Control and Prevention, Stockholm, Sweden
[e] Institution of Medicine, Unit for Infectious Diseases, Karolinska Institutet, Karolinska University Hospital, Huddinge, Sweden
[f] Infectious Diseases, Department of Medical Sciences, Akademiska Sjukhuset, Uppsala University, Sweden

ARTICLE INFO

Article history:
Received 16 September 2009
Received in revised form 27 January 2010
Accepted 1 February 2010
Available online 16 February 2010

Keywords:
Tick-borne encephalitis
TBEV
Immunisation
Vaccine failure

ABSTRACT

Tick-borne encephalitis (TBE) is a major disease of the central nervous system in Europe and is endemic in Sweden with about 200 notified cases annually. The far most effective protective measure against TBE is active immunisation. The vaccines available today induce a high degree of protection in field studies. However, vaccine failures have occasionally been reported and may be overlooked due to different, and sometimes confusing, antibody kinetics in vaccinees with TBEV infection. In this study, 27 patients with clinical and serological evidences of TBE despite adequate immunisation are presented. Vaccination failure is characterized by a slow, and initially non-detectable, development of the specific TBEV-IgM response, seen together with a rapid rise of IgG and neutralising antibodies in serum. The majority (70%) of the patients were more than 50 years of age, which may implicate a need for a modified immunisation strategy in the elderly.

© 2010 Elsevier Ltd. All rights reserved.

1. Introduction

Tick-borne encephalitis (TBE) is one of the most important diseases of the central nervous system in many European countries and is endemic in the southern part of Sweden [1]. As in other areas of Europe, the number of reported TBE-cases has increased during the last two decades. The mortality in Sweden is low (<1%), but morbidity and long time sequelae makes it a disease of great importance in the endemic regions [2,3]. TBE has been reported in Sweden from the laboratories on a voluntary basis since the 1970s and notification is mandatory since 2004. The yearly incidence has been estimated at 3–4/100,000 in endemic regions of Sweden [4]. During the years 2000–2008, between 100 and 224 cases of TBE were reported annually in Sweden despite the fact that vaccination against TBE has been increasing in the exposed population. There are two TBE vaccines on the market; FSME-Immun® (Baxter BioScience) introduced in Sweden 1988 and Encepur® (Novartis Behring Vaccines) introduced in 2003 [5]. The vaccines have since their introduction undergone several modifications.

In Sweden vaccination against TBE is undertaken on a voluntary basis. The vaccination schedule recommended in Sweden follows the recommendations by the manufacturers, with one exception being that after dose four and onwards, a 5-year interval is recommended, irrespective of age. However, all vaccine failures presented in this study occurring after dose 3 or later were seen within 3 years after the previous given dose.

The number of vaccine doses sold in Sweden averages 400,000 annually, but since TBE vaccination is not included in any official vaccination register, the number of immunised individuals is unknown. The protection rate of the vaccine has been estimated to be 96–98% according to field studies in Austria [6]. Vaccination failures have been described, but only few reports have been published to date [7–11].

In 2005, two cases of severe TBE in patients adequately vaccinated against TBE were admitted to the Department of Infectious Diseases, Karolinska University Hospital. The patients were severely ill and were treated at the intensive care unit. Diagnosis was in both cases delayed due to negative TBEV-specific IgM antibodies in their first serum and cerebrospinal fluid (CSF) samples. The presence of TBEV-specific IgG antibodies in acute phase serum was initially interpreted as solely a result from vaccination. Sera and CSF-samples obtained later in the clinical course revealed TBEV-specific IgM, thus enabling a correct diagnosis. These cases focused our interest on the serological kinetics and the clinical picture of patients with TBE despite active immunisation. In this study, data from 27 patients with clinical symptoms and signs of TBE,

* Corresponding author. Tel.: +46 704 413535/8 51779292; fax: +46 8 51771807.
E-mail address: charlotta.rydgard-andersson@karolinska.se (C.R. Andersson).

0264-410X/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2010.02.001

together with serological evidence of TBEV infection despite active vaccination, are presented. The clinical picture, serological findings and implications on the immunisation schedule are presented and discussed.

2. Patients and methods

2.1. Study population

Based on the clinical TBE case reporting in Sweden between 2000 and 2008, patients diagnosed with TBE who had received two or more doses of vaccination against TBE, were analysed retrospectively and their records were carefully scrutinized. The majority of the cases were found in the laboratory and clinical reports to the Department of Communicable Disease Control and Prevention in Stockholm and the Swedish Institute for Infectious Disease Control (SMI).

Patients who had received two or more doses, but not the booster dose in time, and those whose laboratory or vaccination data were incomplete, were omitted. Patients who were diagnosed with TBE less than a month after the second vaccine dose, with a possible exposure to TBEV before vaccination, were also excluded. As adequately vaccinated we considered those who had received two doses or more and were taken ill before the scheduled time for the next dose.

The study was approved by the Regional Ethics Committee.

2.2. Clinical and epidemiological data

For all patients certain epidemiological and clinical data were registered: time spent in a TBE-endemic region and/or known tick bite <1 month before disease onset, number of vaccine doses, the time for vaccination and type of vaccine received. Those vaccinated before 2003 were considered immunised with FSME®, since Encepur® was not available in Sweden prior to this year. Information about the clinical presentation and outcome, as well as data of any underlying immune impairment, chronic illness of significance or use of immunosuppressive drugs was also registered. All information was retrieved retrospectively from existing patient records and, if needed, from telephone interviews with treating physicians and patients.

According to methods described earlier, the severity of disease was classified as mild (mainly meningitis symptoms), moderate (encephalitis; diffuse symptoms and/or one focal neurological symptom) or severe (encephalitis; multi-focal CNS-symptoms) [2,12]. In addition, the presence of any paralysis was noted. Long-term sequelae were not possible to follow systematically due to the study design. Therefore, the outcome was only graded as survival or not, although several patients suffered from substantial sequelae.

2.3. Sample analysis

Pre-existing blood- and CSF-samples from the patients, used for clinical diagnosis, were submitted to extended analysis. Follow-up samples were obtained from some patients in order to verify TBEV infection.

The blood- and CSF-samples, obtained at different time points following onset of TBE-like symptoms, were analysed for IgG antibodies to TBEV using a commercial ELISA, Immunozym FSME IgG (Progen biotechnik GMBH, Heidelberg, Germany), while analysis of TBE-specific IgM was performed by an in-house μ-capture ELISA with peroxidase-labelled TBEV-antigen [13]. A rapid fluorescent focus inhibition test (RFFIT) was used for the detection of TBEV neutralising antibodies (Ab) in sera [14]. Sera and CSF-samples were tested in parallel at 10-fold dilutions starting at 1/100 (serum) and 1/20 (CSF) for IgM and 1/1000 (serum) and 1/100 (CSF) for IgG, respectively. The presence of TBEV-IgM in CSF exceeding a ratio of 1:50 as compared to serum was considered as a sign of intrathecal antibody production. For IgG, all measured optical density values at 450 nm (OD_{A450}) were recalculated according to the manufacturer's instructions. Arbitrary titre calculation was based on the cut-off values for positivity as provided by the manufacturer, yielding a cut-off at OD_{A450} of approximately 0.450. An estimation of intrathecal TBEV-IgG was made by comparing the titres of paired CSF and serum. If titres differed approximately only 10-fold, (CSF < serum) this was regarded as an indication of intrathecal TBEV-IgG production.

A 4-fold titre rise was regarded as significant for all the included assays.

2.4. Diagnostic criteria

A TBE case was defined as clinical signs and symptoms of meningoencephalitis and, in the majority of cases, elevated CSF leucocytes as well as a virologically confirmed TBE diagnosis. The vaccine failures were classified as verified or probable. In the verified cases the presence of IgM antibodies to TBE virus in serum, and/or detectable intrathecal TBEV antibodies, and/or a significant titre rise of neutralising and/or IgG antibodies in serum were required. The probable cases showed TBEV neutralising and IgM antibodies in the one sample available or in a sample taken early in the clinical course of the disease.

3. Results

A total of twenty-seven patients, 18 males and 9 females, met the inclusion criteria and were classified as verified ($n = 19$) or probable ($n = 8$) vaccination failures, i.e. clinical TBE despite active immunisation. The main results are presented in Table 1.

All patients showed a positive epidemiology, e.g. time spent in TBE-endemic area <1 month before onset of disease and 18 patients (67%) could recall a tick bite. The median age was 59 years (range 7–82). Nineteen out of 27 (70%) were older than 50 years of age, 4 were younger than 25 years. Two were children, 7 and 8 years old, respectively. Six patients had received a basic vaccination with two doses, thirteen patients had a complete vaccination with three doses. In eight patients four or more doses were given. The oldest female patient had received in all 7 doses, with booster doses every 3 years according to schedule. All included patients had received their boosters according to recommendations. Vaccine failures were noted for both available vaccines. The majority of the patients were immunised according to the conventional schedule as recommended by the manufacturers, i.e. 1–3 months between doses one and two. A majority of the patients (22/27) were previously healthy, while five patients had a known underlying impairment of the immune system with chronic disease or immunosuppressive drugs, as indicated in Table 1. The clinical pictures were generally severe. Nineteen patients (70%) were classified as having severe or moderately severe encephalitis. Out of these, five were treated in the intensive care unit (ICU) (patients 2,3,4,10 and 13 in Table 1) for 7, 36, 1, 1 and 164 days respectively. Patient 10 was classified as having mild infection due to mainly meningeal symptoms, but was admitted in the ICU due to low blood pressure and atrial fibrillation. One patient was in a specialised stroke unit for 4 days. The rest ($n = 8$) were classified as having mild disease with mainly meningeal symptoms. One third of the patients developed paralysis of some degree.

No patient in the study-group died from TBE in the first year, but one patient, aged 70 years, with an underlying chronic disease (patient 13 in Table 1) succumbed 1.5 years after the acute infection due to severe sequelae.

Table 1
Classification, age, number of TBE vaccine doses, laboratory findings, clinical picture, underlying disease and vaccine type of 27 patients with TBE despite active immunisation.

Patient	Vaccine failure	Age	No. of doses	Time since last dose, months	Positive serum IgM	Positive NT first serum	Significant serum titre rise IgG/NT	Intrathecal antibody production	Clinical picture, mild/moderate/ severe encephalitis	Pareses	CSF findings	Known immune impairment	Vaccine type (number of doses)
1	Verified	64	4	4	Yes	Yes	Yes	Yes	Mild	Yes	pleo	No	NA (2), FSME(2)
2		55	4	16	Yes	Yes	Yes	Yes	Severe	Yes	pleo	No	FSME (4)
3		63	4	24	Yes	Yes	Yes	Yes	Severe	Yes	pleo	No	FSME (3), Encepur (1)
4		7	3	14	Yes	Yes	Yes	Yes	Severe	No	pleo	No	FSME (2), Encepur (1)
5		67	3	24	Yes	Yes	No	Yes	Severe	Yes	pleo	No	NA (2), FSME (1)
6		62	3	27	No[a]	Yes	Yes	Yes	Moderate	No	pleo	No	Encepur (3)
7		39	2	1.5	Yes	Yes	Yes	Yes	Severe	Yes	pleo	No	FSME (2)
8		54	2	5	Yes	Yes	Yes	Yes	Mild	No	pleo	Yes[b,c]	Encepur (1), FSME (1)
9		21	2	15	Yes	Yes	nd[d]	Yes	Moderate	No	pleo	No	Encepur (2)
10		82	7	26	Yes	Yes	Yes	No	Mild	No	pleo	No	FSME (6), Encepur (1)
11		68	5	35	Yes	Yes	Yes	nd[e]	Moderate	Yes	pleo	No	FSME (5)
12		52	5	36	Yes	Yes	Yes	No	Moderate	No	pleo	Yes[b,c]	FSME (3), NA (2)
13		70	4	24	Yes	Yes	Yes	No	Severe	Yes	pleo	Yes[b,c]	FSME (4)
14		66	3	3	Yes	Yes	Yes	No	Moderate	No	pleo	No	FSME (3)
15		62	3	16	Yes	Yes	Yes	No	Severe	No	pleo	No	FSME (1), NA (1), FSME (1)
16		69	3	17	Yes	Yes	Yes	No	Moderate	No	pleo	Yes[b,c]	FSME (3)
17		19	3	28	Yes	Yes	Yes	No	Mild	No	pleo	No	FSME (3)
18		38	3	29	Yes	Yes	Yes	No	Mild	No	pleo	No	FSME (3)
19		46	2	2	Yes	Yes	Yes	No	Moderate	Yes	pleo	No	FSME (2)
20	Probable	8	4	4	Yes	Yes	nd[d]	No	Severe	No	pleo	No	FSME (4)
21		58	3	15	Yes	Yes	nd[d]	No	Severe	No	pleo	Yes[f]	NA (3)
22		61	3	16	Yes	Yes	No[g]	nd[h]	Mild	No	nd	No	FSME (3)
23		58	3	18	Yes	Yes	nd[d]	No	Moderate	No	pleo	No	FSME (3)
24		78	3	20	Yes	Yes	nd[d]	nd[h]	Moderate	No	pleo	No	FSME (3)
25		59	3	25	Yes	Yes	No	No	Mild	No	pleo	No	Encepur (3)
26		66	2	3	Yes	Yes	nd[d]	nd[h]	Moderate	No	nd	No	FSME (2)
27		20	2	7	Yes	Yes	nd[d]	nd[h]	Mild	No	pleo	No	FSME (2)

NT = neutralisation test.
nd = not done.
CSF = cerebrospinal fluid.
NA = vaccine type not available.
pleo = pleocytosis.
[a] IgM just under cut-off.
[b] Rheumatic disease.
[c] Immunosuppressive treatment.
[d] Only one serum taken.
[e] Sera + CSF taken different days; cannot be calculated.
[f] Mb Crohn, kidney failure, hemodialysis.
[g] Significant decrease in IgM over 3 months.
[h] No CSF available.

Analysis of TBEV-IgM was negative for the first serum samples of 4 patients sampled 4–10 days post-onset of symptoms, while a borderline activity was observed for 11 patients (sampling range 1–10 days post-onset). Only 11/27 patients were TBEV-IgM positive in their first sample (sampling range 1–24 days post-onset). One patient did not develop detectable TBEV-IgM. All patients had detectable TBEV-IgG and neutralising antibodies in their first sera, with significant titre rises for 17/20 patients with more than one serum sample available (Table 1). A strong IgM response, a significant IgM titre rise or intrathecal IgM production was observed in 3/20 patients with more than one serum sample available, but in whom significant TBEV-IgG and neutralising antibody titre rises were not demonstrated. In the 8 cases with a probable vaccine failure the importance of adequate sampling is highlighted: only one serum or inadequately spaced sera were taken (all of them TBEV-IgM positive according to selection criteria). Thus additional confirmative evidence, i.e. rising antibody activity in serum or demonstration of intrathecally produced TBEV antibodies (no CSF available), could not be obtained.

4. Discussion

Active immunisation against TBE has been successful in reducing TBE and field data have shown high protective effectiveness [5,6]. However, vaccine failures are likely to appear for most vaccines as a protection rate of 100% is extremely difficult to achieve. The rate of failure cannot be calculated from this study, since the actual number of vaccinated individuals in Sweden is not known.

In our study the vaccine failure is characterized in most cases by a typical secondary antibody response, i.e. a slow IgM response accompanied by a rapid rise of IgG and neutralising antibodies in individuals with prior immunisation against TBEV. This is in accordance with previous findings [7–10,15] as well as the recent report by Stiasny et al. [11], which describes similar immune responses in previously vaccinated TBE patients from Austria, where the serological profile in these patients was clearly different from that in unvaccinated TBE patients, who had a comparatively rapid TBEV-IgM response. The presence of TBEV-IgG and neutralising antibodies in the absence of TBEV-IgM may be falsely interpreted as post-vaccination immunity. This is an important observation, since these patients are easily overlooked if only a single serum is analysed. The true rate of vaccination failures may thereby be underestimated. When TBE-vaccinated patients present with symptoms consistent with TBE, follow-up sera, and preferably also CSF, are necessary to confirm or exclude TBEV as cause of disease. A positive TBEV-IgG, and negative IgM test on clinical presentation does not exclude TBE in an immunised individual. It could be argued that TBEV-IgM responses in patients who have received their first two vaccine doses less than 6 months before disease onset could be vaccine induced [16]. We have, however, not observed IgM responses in a group of vaccinees ($n = 25$) who were tested before and after their 3 first doses (our unpublished observations). It is noteworthy that the correct diagnosis may require a spectrum of TBE assays, which are not available in the routine set up e.g. neutralisation tests and optimal IgM/IgG capture assays for demonstration of intrathecal antibody production [7].

In young adults, and especially children, the vaccines on the market today produce a satisfactory and, according to data at hand, a high protective antibody response [17]. There are few publications on TBE despite vaccination in children [6,18,19]. The youngest patients in this study were only 7 and 8 years old, and had received three doses of vaccine, according to the manufacturer's schedule. Vaccine failures evidently occur at all ages but with a significant dominance for individuals aged 50 years or more. The immunological responsiveness to vaccination decreases with age and may increase the risk for vaccine failures in the elderly as described earlier [20,21]. In view of these findings supported by the well-known reduced antibody response in the elderly [21] alternative primary immunisation schedules may be warranted for this age group.

The intervals between doses are likely to be important. According to earlier findings the so-called fast-track immunisation schedule, with a shortened interval between doses one and two, produces lower antibody levels than the conventional scheme [22,23] and should definitely be avoided in the elderly, and if used, the third dose should be given the same season.

The clinical course of TBE in immunised subjects has not been proven to be more severe as compared to what is observed in unvaccinated patients, although an enhanced severity has been reported in single cases [2,8,24,25]. Whether suboptimal antibody levels may aggravate the disease in accordance with the phenomenon antibody dependent enhancement (ADE), as described for dengue, has not been fully investigated [26–28] and the relevance of ADE in TBE still remains uncertain. In this study, the majority of the patients (70%) had severe or moderately severe encephalitis and only a smaller proportion had mild disease. This could be due to a selection bias where more severe cases are investigated more thoroughly for etiology, while milder cases are not diagnosed as vaccine failures.

Although this study is, to our knowledge, the largest study reported to date on vaccine failures, the number of subjects is still too few, and the study design inappropriate, for any definite conclusions concerning the severity of illness in TBE vaccinees. However, our study clearly demonstrates that very severe encephalitis may occur even in fully and adequately vaccinated individuals and that TBE remains an important differential diagnosis in these patients. Furthermore, the interpretation, sampling, and broad set up of TBE serodiagnostic methods may be required in order to find the true etiology.

Acknowledgement

We are grateful to Marianne Forsgren for critical reading of the manuscript and fruitful discussions concerning the interpretation of the serological assays.

References

[1] Lindquist L, Vapalahti O. Tick-borne encephalitis. Lancet 2008;371(May 31 (9627)):1861–71.
[2] Gunther G, Haglund M, Lindquist L, Forsgren M, Skoldenberg B. Tick-borne encephalitis in Sweden in relation to aseptic meningo-encephalitis of other etiology: a prospective study of clinical course and outcome. J Neurol 1997;244(April (4)):230–8.
[3] Holmgren EB, Forsgren M. Epidemiology of tick-borne encephalitis in Sweden 1956–1989: a study of 1116 cases. Scand J Infect Dis 1990;22(3):287–95.
[4] Gustafson R, Svenungsson B, Gardulf A, Stiernstedt G, Forsgren M. Prevalence of tick-borne encephalitis and Lyme borreliosis in a defined Swedish population. Scand J Infect Dis 1990;22(3):297–306.
[5] Gunther G, Haglund M. Tick-borne encephalopathies: epidemiology, diagnosis, treatment and prevention. CNS Drugs 2005;19(12):1009–32.
[6] Heinz FX, Holzmann H, Essl A, Kundi M. Field effectiveness of vaccination against tick-borne encephalitis. Vaccine 2007;25(October 23 (43)):7559–67.
[7] Günther G, Haglund M, Linquist L, Sköldenberg B, Forsgren M. Intrathecal IgM, IgA and IgG antibody response in tick-borne encephalitis. Long term follow-up related to clinical course and outcome. Clin Diagn Virol 1997;8(May (1)):17–29 [Erratum in: Clin Diagn Virol 1997 Aug;8(2):167–8].
[8] Bender A, Jager G, Scheuerer W, Feddersen B, Kaiser R, Pfister HW. Two severe cases of tick-borne encephalitis despite complete active vaccination – the significance of neutralizing antibodies. J Neurol 2004 Mar;251(3):353–4.
[9] Kleiter I, Jilg W, Bogdahn U, Steinbrecher A. Delayed humoral immunity in a patient with severe tick-borne encephalitis after complete active vaccination. Infection 2007 Feb;35(1):26–9.
[10] Lotric-Furlan S, Avsic-Zupanc T, Strle F. Tick-borne encephalitis after active immunization. Int J Med Microbiol 2008;298(S1):309–13.
[11] Stiasny K, Holzmann H, Heinz FX. Characteristics of antibody responses in tick-borne encephalitis vaccination breakthroughs. Vaccine 2009 Nov 23;27(50):7021–6.

[12] Mickiene A, Laiskonis A, Gunther G, Vene S, Lundkvist A, Lindquist L. Tick-borne encephalitis in an area of high endemicity in Lithuania: disease severity and long-term prognosis. Clin Infect Dis 2002;35(September 15 (6)):650–8.
[13] Holzmann H. Diagnosis of tick-borne encephalitis. Vaccine 2003;21(Suppl. 1):S36–40.
[14] Vene S, Haglund M, Vapalahti O, Lundkvist A. A rapid fluorescent focus inhibition test for detection of neutralizing antibodies to tick-borne encephalitis virus. J Virol Methods 1998 Jul;73(1):71–5.
[15] Kaiser R, Holzmann H. Laboratory findings in tick-borne encephalitis – correlation with clinical outcome. Infection 2000;28(March–April (2)):78–84.
[16] Hofmann H, Kunz C, Heinz FX, Dippe H. Infection 1983;11(May–June (3)):164–6.
[17] Witterman C, Schöndorf I, Gniel D. Antibody response following administration of two paediatric tick-borne encephalitis vaccines using two different vaccination schedules. Vaccine 2009;27:1661–6.
[18] Fritsch P, Gruber-Sedlmayr U, Zoehrer B, Mutz I, Spork D, Zenz W. Tick-borne encephalitis in Styrian children from 1981 to 2005: a retrospective study and a review of the literature. Acta Paediatr 2008 May;97(5):535–8.
[19] Kunz C. TBE vaccination and the Austrian experience. Vaccine 2003 Apr 1;21(Suppl. 1):S50–5.
[20] Hainz U, Jenewein B, Asch E, Pfeiffer KP, Berger P, Grubeck-Loebenstein B. Insufficient protection for healthy elderly adults by tetanus and TBE vaccines. Vaccine 2005;23(May 9 (25)):3232–5.
[21] Rendi-Wagner P, Paulke-Korinek M, Kundi M, Wiedermann U, Laaber B, Kollaritsch H. Antibody persistence following booster vaccination against tick-borne encephalitis: 3-year post-booster follow-up. Vaccine 2007;25(June 28 (27)):5097–101.
[22] Schondorf I, Beran J, Cizkova D, Lesna V, Banzhoff A, Zent O. Tick-borne encephalitis (TBE) vaccination: applying the most suitable vaccination schedule. Vaccine 2007;25(February 9 (8)):1470–5.
[23] Vene S, Haglund M, Lundkvist A, Lindquist L, Forsgren M. Study of the serological response after vaccination against tick-borne encephalitis in Sweden. Vaccine 2007;25(January 4 (2)):366–72.
[24] Bender A, Schulte-Altedorneburg G, Walther EU, Pfister HW. Severe tick borne encephalitis with simultaneous brain stem, bithalamic, and spinal cord involvement documented by MRI. J Neurol Neurosurg Psychiatry 2005;76(January (1)):135–7.
[25] Huisman W, Martina BE, Rimmelzwaan GF, Gruters RA, Osterhaus AD. Vaccine-induced enhancement of viral infections. Vaccine 2009;27(January 22 (4)):505–12.
[26] Boonnak K, Slike BM, Burgess TH, Mason RM, Wu SJ, Sun P, et al. Role of dendritic cells in antibody-dependent enhancement of dengue virus infection. J Virol 2008;82(April (8)):3939–51.
[27] Ferenczi E, Ban E, Abraham A, Kaposi T, Petranyi G, Berencsi G, et al. Severe tick-borne encephalitis in a patient previously infected by West Nile virus. Scand J Infect Dis 2008;(April 7):1–3.
[28] Bröker M, Kollaritsch H. After a tick bite in a tick-borne encephalitis virus endemic area: current positions about post-exposure treatment. Vaccine 2008;26(February 13 (7)):863–8.