EDITORIAL

SURVEILLANCE OF TICKBORNE ENCEPHALITIS IN EUROPE AND CASE DEFINITION

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The study by Stefanoff et al [1] raises two important questions concerning tickborne encephalitis (TBE) virus infections. First, the lack of a generally accepted case definition and secondly the quality of national surveillance of TBE cases. Ideally, reported cases should be confirmed and the clinically relevant cases with central nervous system (CNS) disease should be separated from febrile cases without CNS manifestations. The surveillance of TBE in the European countries is not uniform and not always mandatory. Efforts to reach a final diagnosis, especially in less severe cases and in children, varies as well as the awareness of the disease in low endemic regions. The only relevant and stable basis for national surveillance is cases with established CNS disease, although immunity to TBE virus after less severe febrile illness is of interest on individual basis. The ratio of non-CNS disease to CNS disease is generally believed to be about three, but there are regional differences in virulence. Significantly, age related differences are basically unknown.

Serological diagnosis of TBE can cause problems. Cross reactivity due to previous flavivirus vaccination or infection or a tests with low sensitivity or specificity may affect diagnostic precision. Using standardised enzyme-linked immunosorbent assay (EIA) with appropriate controls, at least 96% of TBE cases in the second meningoencephalitic phase of the disease are IgM positive [2]. Old indirect EIA tests are considered less specific compared to analysis based on microcapture techniques, and generate more false positives. However, more recently developed indirect EIA techniques and immunoblots for TBE diagnosis have both high sensitivity and specificity [2, 3, 4]. In a Swedish prospective evaluation, we found that all TBE cases with specific IgM reactivity on hospital admission could be verified by presence of increased IgG antibody activity in convalescent sera and by intrathecal IgM antibody production [2, 5]. Complement binding reaction with four-fold titre increase in paired sera is an outdated technique that has been replaced by modern EIA technology. TBE antigen detection by virus isolation or polymerase chain reaction (PCR) in the IgM positive phase of the disease is, except for rare positive cases usually post-mortem, negative, and not a useful tool in the diagnosis of TBE [6, 7].

The criteria for a case definition proposed by Stefanoff et al [1] are reasonable. The results and the revision of Polish national surveillance data using the proposed case definition are probably relevant for many TBE endemic countries in Europe. If the discussion is limited to TBE CNS disease, possible cases of TBE will include all cases presenting with meningoencephalomyelitis in a TBE endemic area during the tick season, extended with the longest possible incubation period for CNS symptoms to occur (about four weeks). Consumption of unpasteurised milk products originating from endemic areas should be included in the case definition. Whether cerebrospinal fluid (CSF) pleocytosis is also required in all cases could be debated. In several large consecutive studies on TBE meningoencephalomyelitis, all patients presented with CSF pleocytosis [5, 8, 9,10]. Although not clearly stated, pleocytosis is such an inherent part of the diagnostic process that it almost becomes a compulsory inclusion criteria in these studies. A selection bias with regard to the presence of CSF pleocytosis can therefore not be fully excluded. Nevertheless, TBE associated CNS disease without CSF pleocytosis must be rare, probably even more than in herpes simplex encephalitis. If such cases are encountered, false positive serological diagnosis must be ruled out. Apart from the epidemiological criteria, a possible case could be defined by the presence of specific serum IgM antibodies. Preceding flavivirus disease (visit abroad) or vaccination (TBE, yellow fever and Japanese encephalitis) must, of course, be excluded. TBE IgM antibodies may persist for at least one year [2] and a previous asymptomatic or less apparent TBE virus infection might cause diagnostic problems in a case of non-TBE meningoencephalitis. Based on an estimated maximum yearly TBE seroconversion rate of 1.2-2.4% [11] and a fairly low incidence of non-TBE viral meningoencephalitis, the risk of false positive diagnosis of TBE is of little importance. Diagnosis based on detection of TBE IgM antibodies is, in our opinion, sufficient in routine clinical practice and additional confirmatory tests are not necessary. According to a description of a large consecutive sample of TBE cases, the risk of false negative IgM test in early meningoencephalitic phase was 3 /656 [8]. To overcome this low risk for missed diagnosis of TBE, an additional serum sample could be taken later in the acute phase or during convalescence. An alternative simplified approach could be to analyse acute and convalescent sera for TBE in IgM negative patients not fully recovered at three months follow up in order to establish the diagnosis in the fairly high percentage of TBE cases with long lasting sequelae [2, 10]. Confirmatory tests, which include IgG seroconversion in acute and convalescent sera or detection of intrathecal antibody production could be limited to special cases. The increasing problem of TBE vaccinated patients with possible TBE requires methods for detection of intrathecal antibody production and is an important task for qualified virological laboratories, to detect vaccine failure. Detection of TBE neutralising antibodies is rarely required: only in the few patients where interference with other flaviviruses including vaccines is suspected.

The surveillance of TBE in the European countries is not uniform and not always mandatory

With such a TBE case definition and a reporting system including only cases with TBE meningoencephalomyelitis with, as a minimum requirement, the presence of TBE serum IgM antibodies, reliable and comparable surveillance data between countries and over time will be ensured. Introduction of national systems to detect vaccine failures will further add to quality of the TBE surveillance in Europe.

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EDITORIAL

BLOOD SAFETY AND NUCLEIC ACID TESTING IN EUROPE

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Over the past two decades, a long series of specific and non-specific measures have been introduced into the screening of blood donations in order to reduce the residual risk of transmission of bloodborne viruses. The latest specific measure has been viral nucleic acid testing (NAT), introduced by the European plasma industry in 1995, and subsequently introduced for blood donations in several countries in Europe and elsewhere. NAT was implemented to reinforce the safety of the blood supply; it can detect acute viral infections during the 'window period', that were not being detected by the serological screening methods used at that time. To assess the impact of NAT on the safety of the blood supply, it is essential to estimate the residual risk of viral transmission. In this issue, six European countries (France, Germany, Italy, Spain, Switzerland and the United Kingdom) that have recently implemented NAT describe their experiences and the results of the evaluation of the residual risk of viral transmission in their blood supply [1-6].

In these six European countries, NAT was initially introduced between 1999 and 2001 to detect hepatitis C virus (HCV), probably because the first mandatory screening for plasma used by blood industry was HCV-NAT. In 2001, a publication from an international forum showed that10 out of the 25 countries that now make up the European Union had introduced HCV-NAT for blood screening versus two for HIV-NAT [7]. Later, HIV-NAT was progressively implemented and, Spain is now the only country of the six reported in this issue where this procedure has not yet been introduced. This expansion is probably due in part to the ability to test for both viruses with one of the licensed tests (TMA, Chiron blood testing). France is the only country where NAT was implemented in a single stage for all blood donations collected. In other countries, NAT was first performed on a voluntary basis, before it was made mandatory.

NAT was implemented to reinforce the safety of the blood supply

In Germany, NAT is performed by 'in-house' assay, and the other five countries use one or both of the commercially available nucleic acid amplification methods (polymerase chain reaction (PCR) and transcription-mediated amplification (TMA)), adapted for blood screening. Blood screening strategies differ in the six countries, and there are two levels of heterogeneity in the European practice of NAT. First, the number of blood donations included in pools: these varied between 1 to 96 depending on the country. Second, the variations observed in the procedures used within each country. In France, Germany and the UK, the size of the pool is fixed for each virus, whereas in Italy, Spain and Switzerland, the pool size varies. The variation observed is probably due to the way in which blood donation testing is organised locally. It should be noted that, contrary to the classical serologic screening methods that are always used in single donation testing, current NAT procedures usually demand pooling of blood donation samples due to the format of the employed platforms.

The main aim of introducing NAT in blood testing was the reduction of the residual risk of viral transmission linked to the window period. With the exception of the UK, which has adopted a specific model (see below), each country bases the residual risk estimate on the mathematical model developed by Schreiber et al [8], which takes into account the window period and the incidence rate calculated from seroconversions observed in the repeat blood donor population. However, due to difficulties in obtaining exhaustive data at national level for the calculation of the national incidence rate, most of the contributors have extrapolated from regional or partial data that probably introduce biases. Although widely adopted, this mathematical model has some limitations: it does not take into account the population of first time blood donors or other parameters such as technical or human errors or assay failures that could be implicated in the residual risk. However, this model was validated by the observed yield of NAT [1]. The UK has adapted the Schreiber model by using an adjustment factor in order to evaluate the incidence rate in new donors, by calculating the risk due to test and process errors, and by using different infectious window periods than those currently adopted. It is therefore difficult to compare the results obtained in the UK with those from other European countries.

All countries that analysed trends in the residual risk showed evidence of a decrease. This trend started before the implementation of NAT, probably due to better selection of blood donors and to preventive measures taken in general population to avoid new infections. Before NAT implementation, the residual risk for HCV transmission ranged from 0.64 (France) to 3.94 (Spain) per million donations, with a north-south gradient linked to HCV epidemiology. The residual risk for HIV transmission, excluding the UK, was estimated at between 0.59 (France) and 2.48 (Spain) per million donations. Since NAT implementation, the residual risk for HCV transmission has ranged between 0.1 (France) to 2.33 (Spain) per million donations and for HIV, from 0.18 (Germany) to 1.1 (Italy) per million donations.

Yield rates observed for HIV-NAT are similar in France and Germany (about 0.3 per million donations). The higher rates observed in Italy and the UK may reflect an increased HIV incidence in their donor populations, but a bias due to the small number