SaBTO

Advisory Committee on the
Safety of Blood, Tissues and Organs

POSITION STATEMENT -

WEST NILE VIRUS AND SOLID ORGAN TRANSPLANTATION

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EXECUTIVE SUMMARY

West Nile Virus (WNV) is a blood borne virus spread from animals via mosquitoes. WNV is NOT currently indigenous in the UK, but is endemic in parts of Europe, North America, Australia and other parts of the world. The incubation period of WNV in humans is reported to be 3-15 days. Most human infections are either asymptomatic (76%), or result in only mild flu-like symptoms with full recovery (24%).

There is evidence in the literature that transmission via solid organ transplantation has occurred, but the number of reported cases remains low. As at 2012, 16 recipients are reported to have received organs from 6 donors found to have WNV, leading to 14 infections; amongst these, nine (64%) recipients developed encephalitis and 4 had asymptomatic infection. Not all donors (50%) had detectable WNV viraemia at the time of donation.

WNV infection in the normal population is largely asymptomatic. Overall 1 in 150-200 infected individuals in the general population will develop a more severe form of the disease which may culminate in fatal encephalitis, particularly if they are elderly or immunosuppressed. On the other hand if immunocompromised patients are infected, up to 50% may become symptomatic. In 2012 NHS Blood and Transplant (NHSBT) undertook NAT[1] screening of 28,873 blood donors who had travelled to areas affected by WNV. Despite this travel history, screening revealed no positive cases (ie no detectable viraemia at the time of donation).

Asymptomatic acutely viraemic donors are thought to be the most likely source of identified transmission by organ transplantation. Therefore WNV in organ donors is most likely to be identified where concurrent organ and tissue donation has taken place. Tissue establishments will undertake post mortem testing of donor blood

[1] NAT: Nucleic acid Amplification Technology

where risk factors are identified. This may lead to positive WNV donors being identified following transplantation of organs but prior to transplantation of tissue. Pre-donation screening of organ donors is still controversial and problematic, even in areas of WNV activity. Where screening occurs, results are made available within days of organ transplantation.

There is no effective treatment for WNV. Treatment is largely supportive. Case reports have described clinical improvement with alpha interferon and immunoglobulin (IVIg). Alpha interferon should be used with caution in the early transplant period, following expert microbiological advice. Depending on its provenance, IVIg may not contain sufficient WNV antibody to be effective.

There is no evidence to demonstrate that removal of a grafted organ from a WNV positive donor would prevent progression to encephalitis. Therefore, based on current knowledge and until specific therapy of proven efficacy becomes established, careful clinical and virological monitoring with early diagnosis and supportive intervention appear to be the best available options.

In a recipient who has recently undergone transplant surgery, particularly if there is positive epidemiology, the clinician should consider WNV in the differential diagnosis of a patient presenting with fevers, altered mental status, lower extremity paralysis, Parkinsonian cogwheel rigidity or other neurologic symptoms during the “typical WNV season”, defined as May 1 to November 30.

Serological and molecular assays for the diagnosis of WNV are available. However it is not currently practical or cost effective to screen all organ donors particularly in the absence of indigenous infection in the UK. The current turnaround times for testing and confirmation would in many cases preclude donation.

A recent report suggested that temporary reduction in immunosuppression should be considered in order to allow for restoration of natural immunity to WNV. However there is no current evidence to support this as an effective intervention.

Guidance

- Two dominant scenarios exist for a significant risk of transmission of WNV via organ transplantation:

1. An asymptomatic organ and tissue donor with a finding of WNV viraemia through subsequent tissue donation screening
2. A donor with undiagnosed encephalitis where urgency of transplantation in the recipient has meant that donation has proceeded.

- In cases where NAT testing is positive for WNV and the organs have been used, the details of the positive test should be communicated immediately to NHSBT Organ Donation and Transplantation (ODT) Duty Office (0117 975 7580) who will inform all centres that received organs and/or tissue from the donor. ODT will liaise with appropriate health authorities and all concerned transplant centres.
- Removal of the transplanted organ (even if possible) will not prevent transmission.
- Temporary reduction of immunosupppression has been suggested as it may allow the recipient to mount an immune response to WNV. However, there is no direct evidence to support this as an effective intervention.
- ODT will seek advice from an NHSBT Consultant Virologist on screening and management of donors/recipients prior to disseminating the advice to relevant stakeholders.

Introduction

West Nile Virus is not indigenous in the UK at present, but is endemic in many countries including Southern Europe, North America and Australia.

The Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) has considered the implications should an organ and tissue donor test positive for WNV infection posthumously following the transplantation of an organ.

This paper provides guidance on the management of such a scenario.

About West Nile Virus

West Nile virus is a mosquito-borne flavivirus that is maintained in an enzootic cycle between mosquitoes and birds. Other flaviviruses include Dengue Virus and Yellow Fever Virus[3]. Humans and horses are incidental dead-end hosts because the low level of viraemia in mammals is thought to be insufficient to support further spread via mosquito bites.

Most human infections are asymptomatic and the majority of clinical cases of WNV infections are mild and present with flu-like symptoms, including fever, headache and body aches. In more severe cases, most often observed among elderly and immunocompromised people, there may be signs of encephalitis, meningo-encephalitis or meningitis. In Europe, West Nile virus outbreaks are erratic and spatially and temporally limited phenomena, occurring quite unpredictably, even if all conditions appear to be present in a definite place.

Epidemiology

WNV was first identified in 1937 and since then has been described as infecting humans and horses in many parts of the world. It has been detected in overwintering mosquitoes in the Czech Republic and Romania [6]. Figure 1 describes the reported cases of WNV across Europe. WNV arrived in the USA in 1999 and has since spread rapidly into Canada, Mexico and the Caribbean. It is also endemic in Africa and parts of Australia. WNV outbreaks have been described in both Europe and North America.

The incidence of WNV is probably under-reported. Seroprevalance studies in the USA have documented that 1.7 million individuals were infected over a 10 year period [4].

In temperate climates WNV is seasonal (usually July to September) because mosquitoes need air temperatures above 10° C to function and 15° C to fly. The prevalence of WNV falls during years when there are cold wet summers. Despite WNV being detected in birds and mammals, human seroconversion to WNV is seen less frequently in areas which have maritime climates[7].

WNV in the UK

Culex modestus, one of the species of mosquito that has been implicated in the transmission of WNV, was discovered breeding in marshland in Kent and Essex in 2010 (Figure 2)[8]. This species had not been seen in the UK since 1945. WNV antibodies have been detected in the sera of both resident and migrant birds but live virus has yet to be detected[9].

WNV is not currently detected within the human population in the UK and the incidence of symptomatic WNV in the UK is very low. Public Health England[10] has been conducting surveillance since 2002 and to date only two cases (both from Canada) have been confirmed. In summer 2012, NHSBT screened 28,873 blood donors using NAT testing, which revealed no positive cases of viraemia despite the donors having travelled to areas where WNV has been reported (NHSBT data). Serological data for this cohort are not available.

European Prevalence Data (figure 1) suggest that the nearest place to the UK reporting indigenous cases is the Adriatic coast of Italy.

Clinical Features

The incubation period of WNV is thought to be between 3 and 15 days. Infected individuals are viraemic for up to a week, and may be asymptomatic whilst viraemic.

The majority of infections (c 80%) in humans are asymptomatic. Twenty percent of those infected may develop 'flu like' symptoms and a rash. A small minority (less than 1%) develop meningoencephalitis and/or a poliomyelitis-like syndrome which carries a very high mortality[7]. Elderly individuals and the immunocompromised are more likely to develop neurological symptoms. Chronic infection has also been described whereby replicating virus has been detected in renal tissue up to six years after infection [7].

WNV and Transplantation

There is evidence that WNV has been transmitted via solid organ transplantation (16 recipients are reported to have received organs from 6 donors found to have WNV leading to 14 infections, as at 2012), tissue transplantation and through transfusion of blood products [11,12,13,14,15,]. These cases have either been diagnosed with encephalitis post-operatively or identified through follow up from donors who have been found to be positive after donation. The pattern which emerges from these studies is by no means clear cut. Despite infection proven by NAT testing, some recipients remain asymptomatic with seroconversion, whilst others develop encephalitis with up to 50% mortality.

The incidence of such cases remains extremely low, even in areas where WNV is endemic. However, when WNV is transmitted by solid organ transplantation, encephalitis and/or a poliomyelitis-like syndrome are more likely and carry a higher mortality than in the wider population.

In 2009, 1,248 Italian solid organ donors (WNV is endemic in Italy) were screened for WNV IgM[2] in a retrospective study. Only three (0.24%) were positive. All three were found positive by NAT but none of the recipients were diagnosed clinically with WNV[16]. However NAT testing was not performed on all the donors and the detail of the paper differs from a similar publication in another journal[17]. Other case reports document transmission of WNV from asymptomatic IgM negative, NAT positive donors.

Diagnosis

It is expected that clinicians should include all appropriate pathogens in the differential diagnosis of a patient presenting with fevers, altered mental status, focal weakness, lower extremity paralysis, Parkinsonian cogwheel rigidity or other neurologic symptoms. In the appropriate clinical and epidemiological context, testing for WNV may be indicated and organ and tissues procurement establishments should be made aware of any testing undertaken.

Diagnosis is based on clinical criteria and the presence of the WNV specific IgM in serum or cerebrospinal fluid. NAT testing development has enabled earlier diagnosis of WNV viraemia prior to seroconversion.

[2] IgM: immunoglobulin M, the first antibody that appears in the course of an infection.

In the absence of compatible symptoms and travel risk history, donor screening using NAT testing is not currently recommended for organ donors. WNV NAT screening in the UK is currently only available in reference laboratories at Colindale, Porton Down and Edinburgh and the turnaround time for testing and confirmation would preclude its use for pre-donation screening of the majority of solid organ transplants. Organ-derived WNV transmission has been described where the donor had undetectable viraemia [16], illustrating the fact that serological and molecular testing of the donor is required.

In the UK, organ donors who also donate tissues for transplantation and have a history of recent travel to a WNV endemic area are tested by the tissue establishment for WNV. Should the donor be found to be viraemic at this stage it will be necessary to take appropriate action to manage the situation.

If WNV is identified in a donor from whom organs have been transplanted this information should be communicated to NHSBT, Organ Donation and Transplantation Directorate (ODT). Communication should be via the central Duty Office on 0117 975 7580. The duty office personnel will escalate the incident to ensure that the appropriate health departments, transplant centres and relevant stakeholders are informed. ODT will consult an NHSBT Consultant Virologist to provide guidance on screening and management .

Treatment

Treatment of WNV is largely supportive as there are no anti-viral agents currently found to be effective against it. Case reports have described clinical improvement with alpha inferferon and immunoglobulin[3,4,18] (IVIg) though alpha interferon should be used with caution in the early transplant period, following expert microbiological advice. Dependent on its provenance, IVIg may not contain sufficient WNV antibody to be effective. Animal studies suggest improved survival with WNV infection following treatment with interferon [3]. However, due to concern that interferon may be associated with organ rejection, its use in transplant recipients has not been studied extensively.

There is currently no vaccine therapy available for human use.

A recent report in the American Journal of Transplantation[5] has suggested the temporary reduction of immunosuppression to allow the restoration of natural immunity (if any) to WNV. There is currently no evidence to support this

recommendation, particularly in the UK where WNV is not indigenous and therefore natural immunity is unlikely.

On-going research continues into vaccine therapy (vaccines are currently available for horses) and the use of specific monoclonal antibody therapy.

Conclusion

At present, even in endemic areas the incidence of symptomatic WNV transmitted by organs and tissues remains low. Nevertheless, when WNV is transmitted by solid organ transplantation, encephalitis is more likely and carries a higher mortality than in the wider population.

In geographical areas where WNV has been documented in the human population, evidence suggests that seasonal screening of organ donors could prevent transmission if testing time was sufficiently short to enable a report prior to organ implantation [16].

Given that IgM testing will not exclude active infection, NAT testing would also be required[19]. In the UK, NAT testing is currently only available in three reference laboratories and the turnaround time for testing and confirmation would therefore be likely to preclude its use for pre-donation screening of the majority of solid organ transplants.

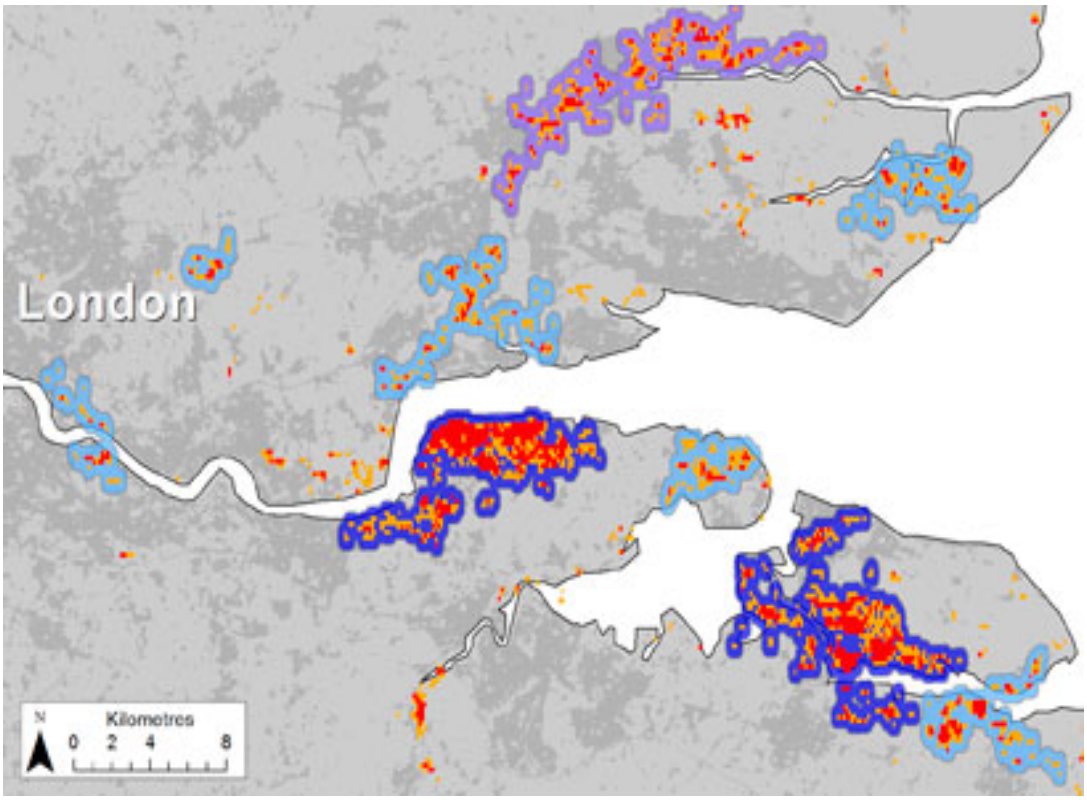
Currently there is no evidence of WNV being detected in the human population in the UK, although there remains the risk that WNV could be transmitted from a donor with a history of recent foreign travel. Seasonal screening of organ donors in the UK is therefore not currently indicated. Rising temperatures as the result of climate change and the presence of *Culex* mosquitoes in the UK may lead to WNV becoming endemic in the UK in the future.

Figure 1: Reported human cases of West Nile Virus for the EU and neighbouring countries, as at 15 September 2011

European Centre for Disease Prevention and Control - RAPID RISK ASSESSMENT – Review of the epidemiological situation of West Nile infection in the European Union – Updated 19th September 2011

www.ecdc.europa.eu/en/healthtopics/west_nile_fever/West-Nile-fever-maps

Figure 2: Map of Thames estuary showing satellite predictions of habitat suitable for Culex modestus



Red dots are most similar and blue represents possible islands of habitat, darker blue being more suitable.

National Environment Research Council – Planet Earth Online – Disease Spreading Mosquito found in UK after 60 years. 9th February 2012

www.planetearth.nerc.ac.uk

Surveillance for Human West Nile Virus in the UK

Since 2002 surveillance for human cases of West Nile virus in the UK has taken place every year between 1st June and 31st October. A case is defined as an adult (particularly those aged 50 years and over) with symptoms of encephalitis, meningo-encephalitis, aseptic meningitis or acute flaccid paralysis, who presents with no travel history outside the UK.

Cases of WNV reported in the UK 2004-2011

Year	Number of Cases	Travel	Reference
2011	0	-	-
2010	0	–	–
2009	0	–	–
2008	0	–	–
2007	1	Canada	HPR 2(6), 8 Feb 2008 p.16-17 in Emerging Infections Update: July-December 2007
2006	1	Canada	HPR 1(6), 9 Feb 2007 p.9-10 in Emerging Infections Update: July-December 2006
2005†	0	–	–
2004†	0	–	–

†Although no cases of WNV were reported in the UK in these years, three cases were reported in residents of the Republic of Ireland (ROI). Two cases in 2004 had travelled to the Algarve in Portugal (Connell et al, 2004) and one case in 2005 had been to the USA. Before 2004 no cases of WNV were reported in either the UK or the ROI. See Related Publications

WNV surveillance began in 2002 but no cases were reported in 2002 or 2003. Health Protection Agency Website. http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/WestNileVirus/Surveillance/

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