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Review

Neglected Australian arboviruses: quam gravis?

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Abstract

At least 75 arboviruses have been identified from Australia. Most have a zoonotic transmission cycle, maintained in the environment by cycling between arthropod vectors and susceptible mammalian or avian hosts. The primary arboviruses that cause human disease in Australia are Ross River, Barmah Forest, Murray Valley encephalitis, Kunjin and dengue. Several other arboviruses are associated with human disease but little is known about their clinical course and diagnostic testing is not routinely available. Given the significant prevalence of undifferentiated febrile illness in Australia, investigation of the potential threat to public health presented by these viruses is required.

Keywords: Arbovirus; Australia; Vector; Transmission; Diagnosis; Undifferentiated febrile illness

1. Introduction

*Ar*thropod-*bo*rne (arbo)viruses, viruses transmitted between vertebrate hosts by arthropods (mosquitoes, ticks, sandflies and midges), present a significant public health risk in Australia and worldwide. More than 75 arboviruses have been identified in Australia [1]. While only relatively few are known to cause disease in humans, there are limited or no data regarding the potential human pathogenicity of the majority of these viruses [2]. Ross River (RRV) and Barmah Forest (BFV) are major alphaviruses that are known to cause a debilitating and sometimes chronic polyarthritis [3]. Murray Valley encephalitis (MVEV) and West Nile Kunjin strain (KUNV) viruses are flaviviruses that cause encephalitis, while dengue (DENV) virus is commonly associated with febrile illness or sometimes haemorrhagic fever [4]. Most arboviruses have a zoonotic transmission cycle that alternates between arthropod vectors and susceptible vertebrate hosts, some of which act as reservoirs of infection in the environment [5,6].

Other Australian arboviruses, such as Sindbis (SINV) Alfuy (ALFV), Edge Hill (EHV), Kokobera (KOKV), Stratford (STRV) and GanGan (GGV), have been associated with human disease [4]. However, they appear to cause predominantly mild symptoms and no outbreak of any has yet been described. SINV is the most common isolate from mosquitoes [7], but its association with human infection is unclear. Similarly, there are many other arboviruses isolated from arthropods in Australia [6,7], and whose role in human infection is yet to be evaluated. These include the bunyaviruses Akabane (AKAV, Koongol (KOOV), Mapputta (MAPV) and Wongal (WONV), and the reoviruses Corriparta (CORV) and Eubenangee (EUBV).

It has been long since postulated that arboviruses may be responsible for causing some cases of undiagnosed febrile illness (UFI) observed in Australia [8]. Prior to the identification of the now commonly diagnosed RRV in 1959 [9] and BFV in 1974 [10], an aetiological agent could not be determined in patients presenting for medical attention with these infections. Even after the identification of the viruses, it took

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almost 15 years before laboratory tests to diagnose infection with them became widely available. Today, more than half of undifferentiated fevers in Australia still go undiagnosed [11], in many cases because treating doctors may feel the cost of the testing is not warranted or the causative agent is novel, not known to cause human disease or there are no routine diagnostic tests available. In such cases, a possible association could be assumed regarding the role of these viruses to the UFI.

This review describes Australian arboviruses, their isolation and identification, distribution, relationship with hosts and vectors, and the infections/diseases that they are so far known to cause.

2. Arboviruses

Based on a combination of their antigenic or phylogenetic relatedness and their known transmission by arthropods the International Catalogue of Arboviruses lists 538 registered viruses that are absolutely or potentially infectious for humans or domestic animals [1]. Clinically significant arboviruses belong to the families and genera of *Togaviridae* (Alphavirus), *Flaviviridae* (Flavivirus), *Bunyaviridae* (Bunyavirus), and *Reoviridae* (Orbivirus) [12]. Some of the other arboviruses that are considered pathogenic to domestic and wild animals are classified as *Rhabdoviridae* (e.g. mosquito/sandfly-borne bovine ephemeral fever), *Orthomyxoviridae* (tick-borne Thogoto virus) and *Asfarviridae* (tick-borne African swine fever virus) [13].

More than 130 arboviruses cause mild to fulminant disease in humans [6]. Most are transmitted in zoonotic cycles, i.e. the principal vertebrate host is an animal other than a human. The distribution of arthropod-borne viruses is restricted by the areas inhabited by their reservoir and vector hosts [4,6]. Thus, many arboviruses have tightly defined ecological zones, while some are distributed globally.

3. Australian arboviruses

In the Arbovirus Catalogue maintained by the US Centers for Disease Control and Prevention (CDC) [1], around 75 viruses are described from Australia (Table 1). In terms of causing disease in humans, the most important are RRV, BFV, MVEV and KUNV [7]. Similarly, SINV, ALFV, EHV, KOKV, STRV and GGV are also recognised as being able to cause disease in humans [14].

3.1. Epidemiology and geographical distribution of Australian arboviruses

The Australian National Notifiable Diseases Surveillance System received notification of 43,811 cases of vector-borne diseases for the 5-year period between 2010 and 2014, the latest year for which data are available [15]. The alphaviruses BFV and RRV accounted for 10,043 (22.9%) and 24,620 (56.2%), respectively, of these. The number of overseas-acquired cases of DENV, almost 10 times higher than those acquired locally, has risen steadily from 219 reported in 2005 to 1716 in 2014 [15]. Population forecasts for Australia predict that the number of people at risk of contracting DENV will grow in future, especially in northern Australia [16]. During the decade 2005–2014, cases of RRV were reported as increasing, in ascending order, from South Australia, Victoria and Western Australia whilst decreasing in Queensland and Northern Territory [15]. Clinical infections with RRV and BFV were detected most commonly in adults, with notification rates higher in the 35–54 year age groups [15]. Most flavivirus infections over this time were due to DENV but cases of MVEV and KUNV were also reported [15]. The overall trend for notifications nationally over the last two decades (1995–2014) is of DENV, BFV and RRV in ascending order (Fig. 1 a) [15].

The prevalence of anti-RRV and anti-BFV antibodies was found to increase with age and was marginally higher among males than females [17,18]. The anti-RRV sero-conversion rate in Queensland has been calculated to be around 1.5% per year, with a significant linear association between age and antibody prevalence [19].

After a long pause, a notable increase in MVEV activity was observed in 2001, 2008 and 2011, in which years there were 6, 4 and 16 clinical cases, respectively (Fig. 1b) [15]. These outbreaks were the largest on record since the 1974 epidemic, a widespread outbreak on the Australian mainland in which 58 patients, the majority of whom lived in Victoria, developed MVEV infections [20]. In addition to these outbreaks MVEV has been identified sporadically in the last 16 years [15]. Unlike the epidemic of 1974, these sporadic cases have occurred not in Victoria but in other parts of Australia, especially in tropical and subtropical regions of Western Australia and Northern Territory. Similarly to MVEV, KUNV is a putative cause of a neurological disease syndrome, although the symptoms are milder than those linked to MVEV. In recent years, cases of KUNV infection have been recorded at a low but regular frequency (Fig. 1b) [15]. However, large numbers of patients infected with KUNV, 18 in 2003 and 12 in 2004, were recorded. In 2011 in south-eastern Australia there was an unprecedented outbreak of neurological disease that affected many horses; however, only a single human case was reported during that episode [21,22].

Almost all the Australian arboviruses known to cause human disease have been recovered from the Australian mainland, excluding Tasmania. MVEV, a clinically significant encephalogenic flavivirus, is enzootic in the northern parts of Western Australia and Northern Territory, cycling between waterbirds and *Culex annulirostris* mosquitoes. Spread of MVEV in other parts of Australia outside these foci is thought to be due to movement of infected birds consequent to heavy rainfall and flooding [23]. For instance, significant outbreaks have been reported after flooding of the Murray-Darling river basin and filling of Lake Eyre located in the normally arid interior of south-eastern Australia, allowing migration of infected waterbirds from northern Australia as far south as north-western Victoria [23].