Arboviruses as a Cause of Undifferentiated Febrile Illnesses

Subjects: Infectious Diseases
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*Ar*thropod-*bo*rne viruses (arboviruses) are, by definition, transmitted between vertebrate hosts by biting arthropods (mosquitoes, ticks, sandflies, midges and gnats). Some arboviral infections — notably, dengue, chikungunya, Zika, Japanese encephalitis, yellow fever and West Nile viruses — pose a major public health threat worldwide. Many others are known or thought to lead to acute undifferentiated febrile illness (UFI), of which a significant proportion of cases are not diagnosed. In low-income countries, a diagnosis of UFI is extremely common due to the lack of pathology laboratory resources. Yet, even in high-income nations, which have adequate access to and quality of diagnostic tools, up to one third of pyrexias may be of unknown origin. It has been estimated that between 12-35% of hospitalized patients with UFI die from UFI-associated complications. In this context, identifying the contribution of hitherto less studied arboviruses as potential etiological agents of UFI and prioritizing the development and availability of diagnostic tests may greatly assist in reducing the global burden of UFI-related disease.

Keywords: arbovirus ; undifferentiated febrile illness ; pyrexia of unknown origin ; diagnosis

1. Undifferentiated Febrile Illness and Pyrexia of Unknown Origin

Fever, defined as an abnormally high body temperature (>100 °F, 37.8 °C), is a common symptom of patients seeking healthcare. Due to the non-specific clinical manifestations and a lack of positivity in initial laboratory testing, the cause of fever may not be identified. When the onset of fever is acute and no cause can be found after taking a full history and physical examination of the patient, it is called a UFI. If the UFI continues, it is classified as a pyrexia of unknown origin (PUO), defined in 1961 as an illness of more than three weeks' duration, with fever greater than 101 °F (38.3 °C) on several occasions, the cause of which is not identified after one week of in-hospital investigation [1]. Since this description does not include many self-limiting viral diseases, it was revised in 1991 [2]. The newer definition of PUO has four categories: classical; hospital-acquired; neutropenic (immune-deficient); and HIV-associated. Also, the revision proposed a minimum of three days of hospitalization or at least three outpatient visits before this diagnosis may be made. Most commonly, PUO is the result of infection, malignancy, or non-malignant inflammatory diseases [3].

2. UFI/PUO as a Health Problem

Between 20% and 60% of UFI cases are attributed to infections [2][4][5][6]. The etiological agents of UFI and PUO vary according to the geography and demography of the patients. For instance, in post-industrial countries, self-limited viral infections and infections with bacteria such as *Brucella* spp., *Leptospira* spp., and the atypical mycobacteria are major causes of UFI/PUO. In economically emerging nations, UFI/PUO include illnesses caused by a diverse range of human pathogens including *Mycobacterium tuberculosis*, *Neisseria meningitidis*, systemic *Salmonella enterica* infections, *Plasmodium* spp., DENV, Epstein-Barr virus, cytomegalovirus, and hantaviruses [7][8][9].

In a landmark prospective research in Belgium of patients hospitalized with febrile illness, depending on if and when a final diagnosis was in fact established, an estimated 12–35% were assessed to have died from PUO-associated complications [10]. The cause of the fever remained obscure in 48% of patients with episodic fever, compared to 26% of patients with continuous fever [10]. Prolonged febrile illnesses remain a diagnostic challenge; about one-third to half of PUO cases remain undiagnosed [11][12][13]. In developing countries, a diagnosis of UFI/PUO may result from a lack of laboratory resources but even in a high-income nation like Japan that has excellent diagnostic tools, 28.9% of PUO goes undiagnosed [14].

3. Diagnosis of Arboviral Infection

Australia can be taken as an exemplar of the relative scarcity of information on the identification, diagnosis and potential pathogenicity of arboviruses that circulate naturally in the environment due to an abundant source of both reservoir hosts and vector mosquitoes. It is by no means unique in being home to indigenous — often relatively under-researched — so-called 'neglected' arboviruses. Hence, lessons learnt from the Australian experience in regard to infectious disease diagnosis, notification and prevention may reasonably be extrapolated to other regions. Arbovirus-associated outbreaks occur predominantly in the tropics and subtropics due to the prevailing hot and humid climate that is conducive to the habitation of vector mosquitoes [15].

For almost a decade after the identification of Ross River virus (RRV) in tropical north Queensland, Australia, in 1959 [16], only small numbers of patients were identified as having a clinical infection with this agent, because virologic and serologic diagnostic testing was available only within a research framework using an in-house test. Following the development of a commercial enzyme-linked immunosorbent assay (ELISA) to detect anti-RRV immunoglobulin (Ig)M antibody [17], the number of patients diagnosed annually rose to between 4000 and 6000 [18]. The number of localities from where RRV cases were reported increased almost two-fold from 1985 onwards [19].

Following its identification from the more southern Australian state of Victoria in 1974 [20], a similar experience occurred with the diagnosis of Barmah Forest virus (BFV) infection and its annual notification [21]. Epidemic polyarthritis, the now outmoded term that was then used to describe the autoimmune conditions associated with both RRV and BFV, became a nationally notifiable disease in 1990 [18]. While typically there are around 4500 notifications of epidemic polyarthritis per annum, 9554 cases were reported in 2015 [22]. A reliable diagnostic test is also now available for Murray Valley encephalitis virus (MVEV) but test requests to regional pathology laboratories are usually only made for patients with highly suggestive signs and symptoms [5].

Clinical infections with the less well-recognized native Australian arboviruses West Nile Kunjin (KUNV) [23][24][25][26], Edge Hill (EHV) [27], Gan Gan (GGV) and Kokobera (KOKV) [28][29] can now be confirmed in specialized reference laboratories, but only suspected KUNV-infected cases undergo screening as standard. Beyond these named species, around another 70 different arboviruses have been been isolated from mosquitoes native to Australia [30], some of which are associated with human disease but for which routine tests are currently not available to diagnose infection [31].

4. A Causal Link between Neglected Arboviral Infections and UFI/PUO?

It has been proposed that arboviruses may be responsible for some cases of UFI observed in Australia [32]. While remarkably few systematic studies of UFI or PUO in an Australian setting have been undertaken, those that have been performed suggest that a large proportion of UFI/PUO cases remain undiagnosed (reviewed in [31]). This is despite the now-routine commercial testing for RRV and for BFV. A three-year retrospective study from 2008–2011 of a tertiary referral hospital in North Queensland found 58.8% of patients with UFI had no definitive diagnosis [33]. Neglected indigenous arboviruses may have infected humans regularly for decades, thereby being responsible for at least some of these UFI cases in this tropical north region. The possibility of arbovirus pathogens from Northern Australia causing more wide-scale outbreaks, such as the notified incidences of MVEV in 2001, 2008 and 2011, and the KUNV equine outbreak of 2011 in south-eastern Australia [34], should also be considered. While the horse-derived WNVNSW2011 strain of KUNV not only differed to, but was more virulent than, other KUNV strains that circulated previously in Australia [34], it may be argued that the ecology of this arbovirus changed alongside the emergence of virulence.

The introduction of commercial screening for RRV and BFV led to a highly significant rise in their respective reported rates of infection when compared to historical records [18][21]; these conspicuous examples of unforeseen prevalence may also apply to other arboviral infections. Hence, it is possible that further, neglected, arboviruses — for which diagnostic tests are not yet available outside research laboratories — are a major underlying cause of undiagnosed UFI/PUO cases in Australia. It is probable that this paucity of public health information reflects an under-recognized challenge to residents of other tropical and subtropical countries arising from the capacity of arboviruses to infect humans or to cause disease in humans. For instance, the emerging public health threat posed by Mayaro virus (MAYV), identified recently in the Amazon and other tropical regions of South America [35].

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