Abstract: Chiropractors and other healthcare practitioners primarily concerned with the treatment and diagnosis of disorders of the musculoskeletal system are often presented with patients complaining of extremity joint pain. The signs and symptoms of Ross River and Barmah Forrest arbovirus infections can often be confused with a number of other conditions including local joint infection, rheumatoid diseases and other systemic diseases causing arthralgic or myalgic symptoms. This paper presents a review of the often debilitating conditions caused by the Ross River and Barmah Forest arboviruses. These increasingly common viruses can produce symptoms of arthralgia, fever, myalgia, rash and headache. A systematic review of the structure of these viruses, their epidemiology, clinical manifestations, treatment and prevention are presented.

Key Indexing Terms: Ross River arbovirus, Barmah Forrest arbovirus, arthralgia, myalgia, fever, musculoskeletal pain, joint pain.

INTRODUCTION

Four arboviruses (arthropod-borne viruses), that are members of the alphavirus genus of the family Togaviridae, have to date been isolated in Australia. They are Ross River virus (RRV), Barmah Forest virus (BFV), Sindbis virus (SIN) and Getah virus (GET). All four viruses have been shown to infect humans, and all but GET are pathogenic to man. GET has only been reported to cause disease in horses in Japan. SIN is the most widely spread arbovirus, extending from northern Europe to southern Africa and right through to Asia and Australia. Birds are the major vertebrate hosts, although SIN can infect and cause fever and rash in humans. RRV and BFV are two of the most important arboviruses in Australia, especially in terms of human disease. Both, although being related but distinct viruses, cause similar symptomatology, with epidemic polyarthritis (EPA) being the most common and significant symptom. RRV is responsible for about 90% of EPA cases, with BFV being responsible for the remaining 10%. Consequently, this paper will discuss principally RRV and BFV and their effects.

The symptoms of RRV infection were first described by J R Nimmo, “.... there has occurred a number of cases of a disease which I cannot nail down as any known epidemic, nor cast into the practitioner’s “dust-bin” of diagnosis and name “influenza”. ....There are three main symptoms: pain, skin eruption and general manifestations.” (p549). The virus was first isolated in 1963 from mosquitoes by Doherty et al, then retrieved from an EPA patient in 1981 by Aaskov et al. Three genotypes of RRV have been defined, with each predominating in a different geographical region of Australia. 95% nucleotide sequence homology still exists between the three genotypes, but the significance of the differences with regards to pathogenicity, remains to be determined.

BFV was first isolated from mosquitoes in the summer of 1974 from the Barmah Forest in northern Victoria. It was first suggested to be pathogenic to man in 1988 by Boughton et al, who described three patients with symptoms consistent with arboviral infection, and with retrospective testing of sera, pointed to BFV as the likely causative agent. BFV is an atypical alphavirus, and as such, has been classified as the sole known member of the seventh alphavirus serocomplex. BFV is only found on mainland Australia.

STRUCTURE

The RRV genome consists of single-stranded positive sense RNA that is approximately 11.8 kb long. The genome produces four nonstructural proteins (nsP1-4) and five structural proteins (capsid, 6K and E1-3) with the capsid protein forming a shell that protects the viral genome. E2 contains three neutralisation epitopes (a, b1 and b2), and all three are able to elicit neutralisation antibodies in the host.

BFV genomic RNA is 11,488 nucleotides in length, excluding the poly(A) tail. It has two open reading frames, one coding for four nonstructural proteins, the other coding for five structural proteins. Note that these are designated the same as for RRV, however they differ at the molecular level.
There are enough similarities between the RRV and the BFV genomes to place them in the same genus, although there are some significant differences. For example, the E2 protein of BFV has no N-linked glycosylation sites, whereas all other sequenced alphaviruses do. A 388nt sequence in E2 only displays 49.5% homology with RRV, and BFV shows little serological cross-reaction with other alphaviruses. The differences are significant enough to entitle BFV to occupy its own serological classification.2,9

EPIDEMIOLOGY

Sporadic cases of RRV disease appear in all states of Australia throughout the year, however significant disease incidence tends to occur in epidemics.13 Several epidemics have been reported, the first of course was by Nimmo.5 In 1979/1980, RRV was exported to several South Pacific islands from the east coast of Australia, resulting in one of the largest epidemics recorded. The explosive nature of the epidemic (greater than 50,000 clinical cases), suggested the appearance of a new disease not endemic to these areas. Together with all isolates being a single RRV variant resembling the genotype found on the east coast of Australia, reasonable evidence supports the notion that RRV was exported there. RRV has not been detected in these islands since the epidemic of 1979/1980.2,14

Hawkes et al15 described an outbreak of EPA in NSW in the summer of 1983/1984 with at least 1196 confirmed cases. This was the largest outbreak of EPA since 1956, when there was an estimated 1000-2000 cases in Mildura alone. Almost equal numbers of males and females were affected, with the highest frequency of clinical infection occurring in the 30 to 39 age group. In this outbreak, there was a high proportion of clinical to subclinical infections (257:340 estimated for Griffith), although previous studies have suggested a much lower ratio normally exists (1:50). Hawkes et al15 suggested the variations in ratios may be due to variations in virus virulence, or to differences in the passage of the virus; human-vector-human as opposed to animal-vector-human. At present, one can only speculate. Other epidemics that have occurred in recent history are the 1988/1989 outbreak of RRV disease in the south-west of Western Australia,16 and the RRV outbreak in the north of the Northern Territory in 1990/1991.17

The epidemiological picture for BFV disease is somewhat less clear, with the data collected thus far supporting no firm conclusions. Much smaller epidemics occur, either coinciding with RRV disease, or in the distinct absence of RRV activity.16 Phillips et al18 report 29 cases of clinical BFV infection between July 1988 and March 1989 from Queensland, NSW and Victoria (21 of them from Queensland). They also provide evidence of extensive subclinical infection with a serological study suggesting that 0.23% of the Queensland population is infected with BFV each year. The same study suggested that 0.59% of the Queensland population is infected with RRV annually.

Another ‘epidemic’ of 22 cases of BFV disease was reported from the south-west of Western Australia from August 1992 to March 1994.16 There was no conclusive evidence of BFV activity in this region of WA prior to 1992, with no isolations during 6 years of mosquito surveillance and no diagnosed human cases. This epidemic of BFV occurred in the absence of significant RRV activity, suggesting as yet undescribed subtle differences in the ecology of BFV and RRV. Yet another BFV disease outbreak occurred along the south coast of NSW in 1995.4

Several retrospective serological studies have been conducted in order to estimate the degree of subclinical infection with alphaviruses. Boughton et al tested 16,842 samples of sera collected during 1981 and 1982 from all regions of NSW for the prevalence of alphavirus antibodies. Figures varied from age group to age group and from region to region, however for the entire population tested, 16.9% of males and 11.1% of females had antibodies to alphaviruses. RRV antibodies were found in 2149 samples, SIN antibodies in 145 samples and an unknown alphavirus was found to have infected 152 samples (NB, BFV was not being tested for at this time). No anti-GET antibodies were detected. The Western plains region demonstrated the highest degree of seroprevalence, with 31.5% of under 20 year olds and 50.5% of over 40 year olds having anti-alphavirus antibodies. The township of Bourke had an overall seropositivity rate of 66%. Hawkes et al15 reported that the incidence of RRV seropositivity in NSW has increased almost across the board relative to the study conducted in 1981. Seroprevalence at the time of this study ranged from 72% in Bourke to 25% in Cohnna.

Hawkes et al18 conducted a serological survey to determine the prevalence of BFV infection in NSW. Anti-BFV antibodies were found to be widespread in humans from all regions of NSW, with seropositivity rates significantly higher in males (2.5%) than in females (1.4%). The highest concentration of infections was recorded from the north coast of NSW, (RRV seroprevalence in NSW is highest in the Western plains region). Overall, antibody prevalence rates for BFV were low compared to other alphaviruses, especially RRV.

The numbers of clinical infections are increasing every year, with 1039 cases of RRV disease throughout Australia in 1980/1981.20 to 2602 cases of RRV disease and 756 cases of BFV disease in Australia in 1995.13 However, Wolstenholme14 predicts in the long term, our grandchildren will be infected when they are very young and numbers of clinical cases will decrease.

In 1989 Kay and Aaskov proposed marsupials and especially macropods (wallabies, kangaroos etc), were the main vertebrate hosts in which RRV was normally
manifestations of the Ross River and Barma Forest Arboviruses

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infections however, have been observed in a wide range of both domestic and feral animals. Most authors tend to concur with this proposal although Wolstenholme contests this theory. He states that droughts and winter animal populations are too small to sustain the virus life cycle, and hypothesizes that the virus is passed down generations of mosquitoes through transovarial transmissions. He concedes however, that animal and human infections are probably necessary to increase the number of infected mosquitoes prior to an outbreak.

A study by Lindsay et al determined that in arid regions of Western Australia, RRV may persist for years in desiccation-resistant mosquito eggs. When environmental conditions are appropriate, these eggs hatch into infected mosquitoes which may give rise to localised outbreaks of infection. This study tends to support Wolstenholme’s hypothesis.

There have been three genotypes or topotypes of RRV defined, which are classified types I-III. Genotype I was found in Queensland and north-central NSW. This variant has not been seen since 1976 when it was last isolated in Charleville (QLD). Genotype II predominates in the eastern states of Australia and co-inhabits the north of Australia with Genotype III. All isolates from the south Pacific belong to this category, and it is believed that type II has replaced type I strains. Genotype III is predominantly found in Western Australia though also extends across the north of Australia. Occasionally type II variants are isolated in the south-west region of Western Australia. These incursions however, are probably due to travel of infected humans or beasts, as opposed to this stain taking hold in the region.

CLINICAL MANIFESTATIONS

Symptoms of RRV and BFV diseases are similar, though vary greatly from person to person. By far the most common symptoms noted are arthralgia/arthritis, (usually of acute onset), myalgia, fever, fatigue, rash and headache. Other symptoms that may occur are swollen lymph nodes, anorexia, nausea, diarrhea, vomiting, sore eyes, sore throat and tingling in the palms of the hands or soles of the feet. The most commonly affected joints are the wrists, knees, ankles, fingers, elbows, shoulders and jaw. The joint symptoms are thought to be due to a local cell-mediated immune response rather than a humeral immune response. Lim et al have also shown that macrophages can be productively infected with RRV and were capable of producing virus for over 50 days. They contest that RRV-induced arthritis may be due to persistent productive infection of macrophages. The rash tends to be more common to BFV disease, while the joint symptoms tend to be more severe and last longer with RRV disease. The classic presentation in over 80% of patients with EPA, is with a rash and joint symptoms.

Infection can occur at any age, however clinical infection is most commonly observed in the 20 to 50 age group. Within this age group, the highest incidence is observed in the 30 to 40 age group, and generally with equal numbers of males and females. Children are often subclinically infected, though when symptoms are apparent they are generally milder and last for a shorter period of time.

The duration of symptoms is different for each person, although it appears that at least half will still be intermittently symptomatic after six months, and at least a quarter after twelve months. Up to 10% will have residual symptoms even after two years. Some adults however will recover within 2-6 weeks after the onset of symptoms, and unfortunately it is not possible to predict how each person will react. The fever, nausea and rash usually disappear very early in the disease, and its the arthralgia/arthritis and muscle pain that persists. Permanent joint damage does not appear to be a feature of either disease. Post-infection immunity is conferred to most people, however there has been a few rare cases of re-infection. Additionally, RRV infection does not confer immunity from BFV and vice versa.

The smallest estimate of the incubation period with RRV disease is 7-9 days, but can range from 3-21 days. The incubation period for BFV disease is considered to be the same as for RRV disease.

DIAGNOSIS, DIFFERENTIALS, TREATMENT AND PREVENTION

Diagnosis of RRV disease or BFV disease can be made by recognising the symptoms, especially during an epidemic, however laboratory confirmation should be sought. Paired sera should be obtained, and a rising antibody titre is positive for infection. Haemagglutination inhibition and several immunoassays are widely used to measure antibodies to both viruses. A significant level of rheumatoid factor can interfere with some immunoassays, however more definitive testing can overcome this problem.

Differential diagnoses include rubella, hepatitis B, mumps, pyogenic infections and the rheumatoid group of diseases, for all can have similar presentations to alphavirus infection. Confirmation needs to be sought for management and prognosis can differ greatly.

Treatment is aimed at symptomatic relief using analgesics like aspirin and paracetamol, or other non-steroidal anti-inflammatory drugs. Bed rest and gentle exercises are very important and the patient also needs to guard against depression. One needs to keep in mind that they will eventually get better.

The only way to contract either disease is to be bitten by an infected mosquito, so prevention relies on minimising
the risk of mosquito bites. The use of repellents, especially those containing 5 to 20% DEET are effective, as is wearing long loose clothing. Times when mosquitoes are most active are around dusk and dawn, so one can minimise outdoor activities at these times. Control of backyard mosquito breeding grounds (Anywhere water can be stagnant, eg roof gutters, animal drinking containers etc) is important, and is something simple and safe the resident can do. Some local governments also conduct mosquito control programmes. At present there are no vaccines to prevent either disease.³

Of interest, several unidentified arboviruses that cause EPA-like disease may also be present in Australia. A number of patients with clinically diagnosed EPA during a RRV outbreak proved negative in laboratory tests for all known arboviruses.⁴

CONCLUSION

The clinical signs and symptoms of RRV and BFV may often be confused with other local or systemic conditions producing joint and muscle pain. With the increasing prevalence of RRV and BFV it is essential for primary healthcare practitioners, concerned with the diagnosis and treatment musculoskeletal pain, to at least possess a basic understanding of the epidemiology, pathophysiology and clinical signs and symptoms associated with these diseases.

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