

Avian bornavirus and proventricular dilatation disease

Fact sheet

Introductory statement

Avian bornaviruses (ABVs) are recently discovered viruses whose genotypes infect a wide range of parrots and waterfowl, the canary, and a variety of other avian species. Many infections are asymptomatic, but others result in inflammation of the nervous system, centrally and peripherally. The subsequent disease, known as Proventricular Dilatation Disease (PDD), is often fatal and has had devastating impacts on birds kept in aviaries and causes mortality in some species of wild bird overseas. Because of the ability of ABVs to cause long-term subclinical infections, multiple genotypes of this virus have disseminated globally with the trade in cage birds. Diagnostic tests have been developed to detect ABV infected birds, but even in combination, they are not sufficiently sensitive to detect many infected birds. Two genotypes of this virus have been introduced into Australia and are present in avicultural collections. It is likely that other genotypes are also present, either as introduced pathogens or naturally occurring viruses in native birds. The escape of the introduced genotypes into wild birds poses a significant risk to native parrot and passerine species.

Aetiology

Order (*Mononegavirals*), family (*Bornaviridae*), genus (*Avian Bornavirus*)

Avian bornaviruses are negative-sense, single-stranded, non-segmented RNA enveloped viruses that replicate in the nucleus of infected cells. There are 7 genotypes that have been detected in psittacine birds with genotype 2 and 4 being the most common (Gancz *et al.* 2008; Honkavuori *et al.* 2008). Another genotype (Avian bornavirus - Canada Goose [ABV-CG] has been isolated from Canada geese (*Branta canadensis*) (Delnatte *et al.* 2011). Recent studies have found three new genotypes of ABV in canaries (*Serinus canaria*) from Germany that genetically map into a separate cluster. These viruses have been proposed to be called ABV-C1, ABV-C2, and ABV-C3 (Weissenböck *et al.* 2009b; Rinder *et al.* 2012). A similar genotype has also been identified in a Bengalese finch (*Lonchura striata*) and may represent a fourth genotype within the canary subgroup (Rubbenstroth *et al.* 2013).

Natural hosts

Parrots (*Psittaciformes*)

Avian bornaviruses have either been detected in or suspected to occur, based on histological lesions, in over 80 species of parrot. Avian bornavirus has never been detected in wild parrots, but have been detected in species whose original range would have included the Indopacific, Asia, Africa and Central and South America (Gancz *et al.* 2013, Heffels-Redmann *et al.* 2011). It is very likely that the number of species susceptible to infection is much larger than this and will be documented as more extensive testing occurs. Australian species known to develop PDD or have been detected with ABV infection include the sulphur-crested cockatoo (*Cacatua galareta*), palm cockatoo (*Probosciger atterimus*), red-tailed black cockatoo (*Calyptorhynchus magnificus*), galah (*Eolophus roseicapillus*), gang gang (*Callocephalon fimbriatum*), cockatiel (*Nymphicus hollandicus*), red-capped parrot (*Purpureicephalus spurius*), and eclectus parrot (*Eclectus roratus*) (Gancz *et al.* 2013, Heffels-Redmann *et al.* 2011). It is highly likely that many native Australian species of parrots are susceptible to infection.

Passerines

Three genotypes of ABV (C1, C2, and C3) have been detected in canaries and clinical disease and microscopic lesions resembling PDD have also been described in canaries (Rubbenstroth *et al.* 2013). A fourth similar genotype has been found in a Bengalese finch (Rubbenstroth *et al.* 2013). Proventricular Dilatation Disease has been described in a greenfinch (*Carduelis chloris*), a long-wattled umbrella bird (*Cephalopterus penduliger*), a bearded barbet (*Lybius dubius*), honey creeper, and weaver finch (Perpinan *et al.* 2007).

Swans, geese and ducks

Proventricular Dilatation Disease-like lesions were first reported in Canada geese in 1991 (Dauost *et al.* 1991). Avian Bornavirus-CG has been detected in wild Canada geese and trumpeter swans (*Cygnus buccinator*) and feral mute swans (*Cygnus olor*) in North America (Payne *et al.* 2011b; Delnatte *et al.* 2011, Guo *et al.* 2012; Delnatte *et al.* 2013). Some of these birds were healthy and others were ill and had PDD-like lesions. Additional studies have shown that ABV-CG can also be detected in snow geese (*Chen caerulescens*) and Ross's geese (*Chen rossii*) (Payne *et al.* 2012a, Payne *et al.* 2012b). Avian Bornavirus-CG has also been identified in mallards both domestic and wild (I. Tizard pers. com. 2013). Avian Bornavirus-CG has been isolated from fibroblasts derived from Pekin duck eggs and viral RNA has been detected in Pekin duck eggs from commercial sources, suggesting that ABV-CG is present in these commercial flocks (Payne *et al.* 2012b). Pekin ducks were inadvertently infected with ABV genotype 4 when exposed to infected cockatiels (Gray *et al.* 2009). Pekin ducks have been imported into Australia and could potentially be infected with an ABV genotype.

Other species

Avian Bornavirus RNA has been detected in three species of North American gull (herring gull [*Larus argentatus*], ring-billed gull [*L. delawarensis*] and laughing gull [*L. atricilla*]) (Payne *et al.* 2012b). The virus from the herring gull has been sequenced and is ABV-CG. Avian Bornavirus-CG has also been detected in the brain of a bald eagle (*Haliaeetus leucocephalus*) that died with encephalitis and from a Mississippi kite (*Ictinia mississippiensis*) (Payne *et al.* 2012b). Lesions resembling PDD have also been described in two other raptors, a red-tailed hawk (*Buteo jamancensis*) and peregrine falcon (*Falco peregrinus*) (Shivaprasad 2005). The host

range of ABV-CG and Bornaviruses in general may be fairly extensive as ABV-CG has recently been detected in a razorbill (*Alca torda*), and a yellow-crowned night heron (*Nyctanassa violacea*) (I. Tizard pers. comm. 2013) and PDD like lesions have been described in a toucan (*Rhamphastos* sp.), and roseate spoonbill (*Platalea ajaja*) (Gregory *et al.* 1994).

World distribution

Parrot genotypes of ABV have been documented in North America, South America, Europe, Africa, the Middle East, Japan and Australia and it is likely that these genotypes have disseminated globally as the result of the international trade in wild caught and domestically raised parrots (Kistler *et al.* 2008; Honkavuori *et al.* 2008; Marietto-Goncalves *et al.* 2009; Weissenbock *et al.* 2009a; Heffels-Redmann *et al.* 2011; Ogawa *et al.* 2011). It is a principal threat to the recovery of the last significant population of Spix macaws currently housed in the Middle East (Wyss *et al.* 2009).

The ABV-CG genotype has only been identified in waterfowl and other species in North America (Delanatte *et al.* 2011; Guo *et al.* 2012).

The canary genotype has only been described in canaries from Germany, but it is also likely to have a global distribution. The finch genotype was identified in a common avicultural species of finch in Japan (Rubbenstroth *et al.* 2013).

Occurrences in Australia

There have been no reports of ABV in Australian wild birds. Proventricular Dilatation Disease was first reported in Australia in 1997 in a captive green-winged macaw (*Ara chloroptera*) imported into Australia in 1993 (Sullivan *et al.* 1997). Proventricular Dilatation Disease has subsequently been described in four other imported species including a red-sided eclectus parrot (*Eclectus roratus polychloros*), Moluccan cockatoo (*Cacatua moluccensis*), sun conure (*Aratinga solstitialis*) and African grey parrot (*Psittacus erithacus erithacus*). An informal survey of a group of Australian avian practitioners in late 2008 indicated that 7 of 35 had cases of PDD that were documented by histopathology (Phalen pers. comm. 2013).

Avian Bornavirus-2 was sequenced from tissues from a Moluccan cockatoo from a Queensland aviary (Weissenbock *et al.* 2009a). Avian Bornavirus – 4 has been detected in the tissues of a psittacine bird with PDD. Uncharacterized genotypes of ABV have also been detected in droppings from two other subclinically infected psittacine birds in aviaries on the East Coast of Australia (David Phalen pers. com. 2013).

Epidemiology

There is increasing proof that ABVs are the cause of PDD. In a small study of experimentally infected parrots, Koch's postulates were fulfilled (Gray *et al.* 2010). Disease has also been produced in other less stringently controlled infection studies (Gancz *et al.* 2009; Lierz *et al.* 2012; Piepenbring *et al.* 2012).

The epidemiology of ABV in parrots is complex. Infected birds may develop disease or may not (Payne *et al.* 2011a). Incubation periods between infection and the development of disease may range from a few weeks to many years. Subclinically infected birds may shed virus for years, possibly their entire life (Payne *et al.* 2011). Infected birds may shed virus continuously, intermittently, rarely, and it is possible that some may never shed virus. Virus shedding has been detected in oral secretions and in droppings and virus has been shown to be shed in urine. Viral RNA has also been detected in feathers (Hoppes *et al.* 2010). Given that

there are so many genotypes of ABV and infection can occur in so many species, it is likely that both host and virus factors will ultimately be found to determine the frequency of virus shedding in infected birds and the percentage of birds that will ultimately develop disease. It is also possible that infection with a second genotype may precipitate the onset of disease in subclinically infected birds (Mirhosseini *et al.* 2011; Payne *et al.* 2011a).

In a very limited study, ABV infection was induced with oral inoculation suggesting that virus ingestion is one route of infection. Inhalation of aerosolised particles contaminated with virus is another possible but unconfirmed route of infection.

Viral RNA has been detected in the eggs of infected parrots but not in others (Monaco *et al.* 2012 and Kerski *et al.* 2012), so it is possible that some but not all ABV infected parrots can vertically infect their offspring. Horizontal transmission after hatch is also likely (Kerski *et al.* 2012). Avian Bornavirus was found growing in fibroblasts derived from commercial duck eggs also suggesting that vertical transmission may be possible (Payne *et al.* 2012b).

Current studies suggest that infection prevalence's within flocks of avicultural species can vary substantially from no birds infected up to 28% of birds infected (Heffels-Redmann *et al.* 2011). Disease rates can also vary substantially with no know history of disease in some infected collections to the loss of the majority of a collection over a period of a few years in others. Preliminary data in canary flocks suggests that infection prevalence varies from flock to flock and as will rates of morbidity and mortality (Rubbenstroth *et al.* 2013).

Very little is known about ABV epidemiology in wild birds, other than the increasing evidence that infection in swans, geese and ducks in North America is relatively common, but again prevalence will vary between populations.

Clinical signs

Many, perhaps most, ABV infections do not result in disease. When disease occurs, it is the result damage to the nervous system that may be viral induced or the result of the host response to infection. Signs are typically divided into those caused by damage to the central nervous system and those associated with damage to the nerves controlling the motility of the digestive tract. Signs involving one or both systems may be present in diseased birds.

Signs caused by disease of the central nervous system are typically slow to develop and are progressive. They include, mentation changes, ataxia (loss of balance), a progressive weakness developing into paralysis, seizures have also been reported but are rare (reviewed in Hoppes *et al.* 2010; Gancz *et al.* 2013). Blindness, although rare, can occur as the result of ocular or neurologic disease (Steinmetz *et al.* 2008).

Damage to the nerves of the digestive system results in alterations in gut motility and even paralysis of the gut, this in turn impacts the bird's ability to digest food. Signs of alteration of digestive function include passage of whole seeds in the droppings, diarrhoea, regurgitation, delayed crop emptying and the resultant weight loss. Many birds are emaciated on presentation.

Diagnosis and laboratory procedures

Diagnosis of ABV infection

Diagnosis of ABV infection in the live bird by molecular techniques. Multiple polymerase chain reaction (PCR)-based assays have been described that have been used to detect ABVs in samples collected from live birds. The primers used in these assays need to be designed to detect the specific virus that is expected to be found in the species of bird that is being tested. In some cases, testing with multiple primers may be necessary if all possible ABV genotypes are to be detected (Kerski *et al.* 2012; Hoppes *et al.* 2013).

Avian bornaviruses have been detected in oral and tracheal swabs, cloacal swabs, crop biopsies, blood and feathers (Kerski *et al.* 2012). A full comparison of the sensitivity and specificity of PCR examination of these different tissue samples from the same bird has not been done. Testing is also complicated by the fact that virus shedding can be extremely variable in frequency and amount, and it is likely that many birds shed virus intermittently, rarely, or not at all. Current recommendations for testing include repeated testing of cloacal swabs or droppings (a minimum of three samples), possibly in conjunction with PCR analysis of feathers (reviewed in Gancz *et al.* 2010; Hoppes *et al.* 2013).

Diagnosis of ABV infection in the live bird by detecting antibodies. Some, but not all birds infected with ABV will develop antibodies. Others will go long periods without developing circulating antibodies and then will suddenly develop them (Hoppes *et al.* 2010). It has been postulated that the sudden onset of antibody production may indicate the onset of clinical signs. In contrast many seropositive birds do not show signs of PDD (de Kloet and Dorrestein 2009). Several diagnostic tests have been developed to detect antibodies in the blood of infected birds (de Kloet and Dorrestein 2009, Villanueva *et al.* 2010). ABV produces two proteins (the N and P protein) to which their host may produce antibodies. Studies have shown that antibodies are most likely to be produced against the N protein (Villanueva *et al.* 2010). These antibodies have been detected using Western blot assays and enzyme-linked immunoassays. Immunofluorescent assays using cells infected with ABVs have also been used to detect antibodies (Villanueva *et al.* 2010). If the ultimate goal is to identify infected individual birds, testing sensitivity is improved if both PCR-based testing and antibody testing is done (de Kloet *et al.* 2007; Hoppes *et al.* 2013).

Diagnosis of PDD

Neither the digestive nor neurological signs exhibited by birds with PDD are sufficiently specific to make a diagnosis; therefore other diagnostic testing is required. In advanced cases, plain radiographs demonstrate distension of the proventriculus and ventriculus. These organs may be massively distended. Dilatation of the intestines may also occur, although less frequently. The presence of gas in any part of the digestive tract is abnormal and an indication of altered gastrointestinal (GI) motility. Contrast studies using repeated radiographs or fluoroscopy has proved a very effective way of detecting both subtle and severe changes in GI motility (reviewed in Hoppes *et al.* 2010; Gancz *et al.* 2012).

While signs and imaging findings may be highly suggestive of PDD, currently a diagnosis of PDD can only be made by demonstrating specific inflammatory lesions in affected nerves. Crop biopsies are the easiest and safest means of obtaining tissue that may contain diagnostic lesions, unfortunately only approximately 50% of birds with PDD will have lesions (Graham 1984; Doolan 1994; Gregory *et al.* 1996). Biopsy of a nerve on the serosal surface of the proventriculus or ventriculus is a much more sensitive, but also a much riskier procedure (Graham 1984).

Isolation of avian bornaviruses

Avian bornaviruses are readily grown in cell culture. Cells of quail, chicken, and duck origin have been used to grow bornaviruses (Hoppes *et al.* 2010). Recently, the quail fibroblast cell line CEC-32 has been shown to be an efficient system for isolation of ABVs from parrots (Rubbensroth *et al.* 2012). Avian bornaviruses do not cause cytopathic effects in cells, therefore their presence must be detected PCR assays or immunohistochemistry.

Clinical pathology

Specific haematologic and blood chemistry changes are not associated with ABV infection or the development of PDD. Birds with advanced PDD are typically anaemic and hypoproteinaemic. White blood cells counts can either be normal or elevated, depending on whether there is an overgrowth of bacteria and yeasts associated with the stasis of the digestive tract or there may be a secondary infection present in other body systems. Uric acid levels may be elevated if the bird is unable to get to its water source and becomes dehydrated.

Pathology

Typical necropsy findings include an emaciated bird with a massively distended proventriculus and ventriculus containing ingesta. Myenteric nerves to the proventriculus and ventriculus may be grossly enlarged. Dilatation of some or all of the intestines may also occur. Dilatation of the gastrointestinal tract, however, is not always present. Microscopic lesions include a non suppurative encephalomyelitis, enlargement and lymphoplasmacytic infiltration of the myenteric nerves of ventriculus, proventriculus, crop and intestines in decreasing order of frequency with an associated lymphoplasmacytic infiltration. Similar lesions are found in peripheral nerves (Berhane *et al.* 2012). Inflammation of the nerves of the heart and lymphoplasmacytic infiltration of the adrenals occurs infrequently. Bornavirus can be identified in brain sections and many other tissues, using immune histochemical testing, if the necessary primary antibody is available (Lierz *et al.* 2009; Ouyang *et al.* 2009; Rinder *et al.* 2009; Raghav *et al.* 2010). Currently this antibody is not available in Australia.

Differential diagnoses

Many chronic diseases can resemble PDD. Bacterial and fungal infections of the upper gastrointestinal tract can result in a failure of crop emptying and decreased gastrointestinal motility. Diseases of the ventriculus including fungal and bacterial infections, and cancer can also result in whole seeds being passed in the faeces. Intestinal obstructions can also result in dilatation of the ventriculus and proventriculus (reviewed in Gancz *et al.* 2010; Hoppes *et al.* 2013).

Zinc and lead intoxication cause stasis of the digestive tract in all species and dilatation of the proventriculus and ventriculus in some species of waterfowl. Zinc and lead intoxication will also cause central nervous system signs that resemble those seen in birds with PDD. Vitamin E, thiamine, and vitamin A deficiencies can also cause central nervous system signs resembling that seen in birds with PDD. Microscopically, paramyxovirus 1, 2 or 3, and arboviruses, including West Nile virus can produce brain lesions similar to those caused by ABV (reviewed in Gancz *et al.* 2010, Hoppes *et al.* 2013).

Laboratory diagnostic specimens

In the live bird, blood, droppings, oral swabs and feathers can all be submitted for PCR testing for ABV RNA. All samples should be kept chilled from the time they are collected until the time they are tested. A crop biopsy containing a section with a prominent blood vessel can be used to detect PDD lesions in nerves (Gregory *et al.* 1996; Gancz *et al.* 2010). A second smaller section can be submitted for PCR testing. This section should be frozen until it is tested.

In post-mortem specimens, a complete set of tissues should formalin-fixed and submitted for histopathology. Transverse sections of all levels of the digestive tract should be made. Half the brain can be formalin-fixed and the remainder frozen for PCR testing. Given that not all birds with PDD have ABV present in the brain, a section of ventriculus and proventriculus should also be saved frozen for PCR testing.

Cloacal and pharyngeal swabs, blood, and tissues (brain, crop, proventriculus, and ventriculus have all been used to isolate ABVs. Samples should be tested immediately or frozen (-80 °C) until testing.

Treatment

Currently there are no treatments available that will cure a bird of infection. Treatments, however, have been developed that reversed the signs of PDD. These treatments are most effective in the early stages of the disease, and are unlikely to work in birds with advanced disease.³

Both Celecoxib (Dahlhausen *et al.* 2002) and Tepoxalin (Zubrin; Schering Plough, Union, NJ, USA) (Gancz *et al.* 2010) which are nonsteroidal anti-inflammatory drugs have been shown to reverse the clinical signs and microscopic lesions in birds with PDD. Treatment durations of up to many months may be necessary for resolution of signs. There is anecdotal evidence that the antiviral drug amantadine hydrochloride may also contribute to the recovery of birds with PDD (Gancz *et al.* 2010).

Prevention and control

Preventing the dissemination of ABV infection in captive collections of birds is challenging and may be impossible with current diagnostic techniques. It would require that all birds entering a collection be repeatedly tested by PCR assays and also tested for the presence of circulating antibodies. The latter test is not available in Australia at this time. Even with this intensive level of screening, infected birds have been shown to be negative on both assays so introduction of positive birds into a collection may still occur.

ABV isolates are thought to be stable at neutral pH and can withstand alkaline and acid solutions, inactivated by heat (56°C) for 3 hours, but are stable at 5 °C for 3 months. Their ability to survive in the environment is not known. The virus is enveloped and is assumed to be susceptible to commonly used disinfectants including chlorhexidine, phenolics, quaternary ammonium products and bleach (reviewed in Hoppes *et al.* 2013).

Surveillance and management

Wildlife disease surveillance in Australia is coordinated by the Wildlife Health Australia. The National Wildlife Health Information System (eWHIS) captures information from a variety of sources including Australian government agencies, zoo and wildlife parks, wildlife carers, universities and members of the public. Coordinators in each of Australia's States and Territories report monthly on significant wildlife cases identified

in their jurisdictions. NOTE: access to information contained within the National Wildlife Health Information System dataset is by application. Please contact admin@wildlifehealthaustralia.com.au.

There are currently no formal surveillance programs for ABV in place in Australia and there is no AUSVETPLAN for PDD and bornavirus. However, any cases of ABV in wildlife would fit within the general surveillance category of “Interesting or unusual cases” and should therefore be captured by AWHN wildlife coordinators as part of Australia’s general wildlife surveillance system (www.wildlifehealth.org.au).

Research

It is likely that the current understanding of ABVs is just the tip of the iceberg and that many new genetic strains will be found in many different species of birds. Nothing is known about the extent that ABV has spread in aviculture in Australia and identifying its distribution by serologic or PCR-based assays would help to understand what impact it is having on the avicultural industry and the risk that it might pose to native species.

It is very likely that the host range of the ABV canary variants will extend beyond the canary and could include native Australian finches (Rubbenstroth *et al.* 2013). Given that these finches are often kept in mixed aviaries with canaries it is possible that cross species infection will occur and this merits further investigation.

Given the detection of ABVs in a range of wild birds in North America and the domestic Pekin duck and mallard, it is likely enzootic and introduced genotypes of ABVs are present in Australian wildlife. Testing for these viruses in any cases of birds exhibiting PDD-like signs or lesions is indicated.

Human health implications

There have been no reports of ABV in humans and its zoonotic potential is unknown.

Conclusions

Avian bornaviruses are composed of a genetically heterogeneous population of viruses that infect a wide range of avian species. Their impact on captive-raised parrots has been, at times, catastrophic and they threaten captive breeding and reintroduction programs for endangered species of parrots. Avian bornavirus 2 and 4 have been introduced into Australia as the result of the parrot trade and it is likely that other ABVs have also been introduced by importation of passerine species including the canary and ducks such as the Pekin duck and the mallard. Release of these viruses into wild populations of native Australian species or transfer to captive breeding populations of endangered species could have significant negative consequences.

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To provide feedback on this fact sheet

We are interested in hearing from anyone with information on this condition in Australia, including laboratory reports, historical datasets or survey results that could be added to the National Wildlife Health Information System. If you can help, please contact us at admin@wildlifehealthaustralia.com.au.

Wildlife Health Australia would be very grateful for any feedback on this fact sheet. Please provide detailed comments or suggestions to admin@wildlifehealthaustralia.com.au. We would also like to hear from you if you have a particular area of expertise and would like to produce a fact sheet (or sheets) for the network (or update current sheets). A small amount of funding is available to facilitate this.

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