Clinical courses and neurological signs of canine distemper virus infection in dogs

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Independent of the occurrence of neuropathological lesions, nervous infection by canine distemper virus (CDV) may lead to a variety of neurological signs observed singly or in combination; these signs include behavioral changes, focal to generalized seizures, cerebellar and vestibular signs, visual deficits, paresis and paralysis, tremors and limb weakness, myoclonus, and signs of leptomeningitis such as cervical rigidity and generalized hyperesthesia. The clinical neurology of CDV infection covers many areas and the neurological signs are diverse. The authors have been working with both conventional and non-conventional neurological presentations of distemper in dogs for years, and in this mini-review different clinical courses and neurological signs of nervous distemper will be presented and discussed.

Keywords dog; canine distemper virus; central nervous system; clinical neurology; neurological signs; nervous distemper

1. Introduction

Canine distemper is an old and well-characterized viral disease that has been known to affect dogs and other carnivores worldwide for centuries. However, despite the use of vaccination strategies for control, it remains as an important viral disease in dogs. Additionally, distemper is the infectious viral disease with the highest fatality rate in dogs besides rabies. The disease has become comparatively rare in many developed countries due to vaccination [1]. Nevertheless, it exists even within vaccinated populations [2, 3]. Norris et al. [4] described distemper as "re-emergence of an old enemy".

Canine distemper virus (CDV) is a non-segmented single-stranded negative sense RNA virus that belongs to the *Paramyxoviridae* family and has been classified in the *Morbillivirus* genus. The virion is relatively large (150-240 nm) and surrounded by a lipoprotein envelope derived from virus glycoproteins that incorporate into the cell membrane [5]. The virus induces a multisystemic infection that is associated with viral spread to the central nervous system (CNS), often resulting in a progressive and multifocal central nervous system (CNS) disease [6, 7].

2. Clinical course of canine distemper virus infection

In dogs, CDV infection may result in subclinical infection or clinical disease. It is estimated that 25 to 75% of the infections occur as subclinical infections. The clinical disease has been characterized by systemic signs (dermatological, respiratory, and gastrointestinal) with frequent nervous dysfunction [8].

According to the classical literature, CDV infection may lead to neurological involvement simultaneously with systemic involvement or 1 to 3 weeks after the resolution of the systemic signs [8, 9]. However, nervous distemper was observed in dogs with molecular RT-PCR-based diagnosis of CDV 3 to 4 months after the initial systemic signs [10]. In addition, dogs that initially presented with neurological manifestation showed systemic signs 1 to 2 weeks later [11]. Furthermore, neurological presentation may be the only clinical sign of CDV infection [12-14].

The course and outcome of the disease as well as the type of neuropathological presentation are directly related to the virus strain, as well as to host factors such as age and the immunocompetence of the affected animal [15-17]. However, the age and immunocompetence of the dog may be the main determinant of the clinical and pathological presentation. Outbreaks of nervous distemper with different clinical presentation and outcome have been observed; phylogenetic analysis of the whole hemagglutinin (H) gene showed that the etiological agents were wild-type CDV strains with high similarity [18, 19].

The clinical diagnosis of nervous distemper has been often performed when systemic signs precede or accompany the neurological disease [20]. Myoclonus is also often seen with CDV infection [21, 22] and has been widely used for the clinical diagnosis of nervous distemper. However, such clinical criteria for diagnosis of nervous distemper should be considered with caution. Although most cases of nervous distemper will have conventional presentations, neurological disease in the absence of both systemic illness and myoclonus may be observed [11, 13, 14].

According to Tipold et al. [17], systemic involvement may be absent in almost 1/3 of the cases, and myoclonus may be absent in more than half of the cases. Intermediate titers of antibodies may protect animals from systemic disease but are not sufficient to block nervous tissue infection. In addition, systemic involvement may be observed with other infectious conditions of the CNS, and myoclonus has also been reported with nervous system diseases other than

distemper. Mariscoli and Jaggy [23] showed that the regressed history and the development of extraneural signs were not useful for differentiation of nervous distemper from other inflammatory or infectious diseases of the CNS. In addition, myoclonic-like movements may be observed in conditions of the CNS other than CDV infection [11, 23].

Distemper encephalomyelitis usually is a multifocal neurological disease in which the clinical and neuropathological findings reflect the wide virus and lesion dissemination in the CNS [7]. However, neurological signs in dogs with distemper may suggest a restricted localization of the lesion within the CNS [10, 17, 22] with a single distinct neurological syndrome.

The recognition of a multifocal nervous disease might suggest an inflammatory disease such as distemper. In such a clinical situation, differential diagnosis should be carried out for other nervous diseases, mainly those with inflammatory/infectious etiologies. Although the most cases of nervous distemper have a predictive course with multifocal nervous signs, in some instances distemper may present with acute onset of focal nervous signs [11, 24], confusing the veterinarian.

In areas where CDV is endemic, the virus should be always considered as an important differential diagnosis for dogs with neurological dysfunction, independent of the type, course, extension, and nature of the nervous disease. During the last 8 years the authors have been studying dogs presenting with central nervous disease, and an effort has been made to diagnose or even exclude CDV infection in such cases [11, 13, 14, 18, 19, 25-32]. Distemper has been observed to mimic other neurological diseases (clinical and neuropathological aspects) and other nervous conditions mimic the expected neurological and neuropathological findings of CDV infection [10]. Other CDV-free inflammatory and degenerative nervous conditions were diagnosed *post mortem*, even when a typical course suggestive of CDV infection was recorded. In addition, nervous conditions other than distemper were already diagnosed in dogs presenting with myoclonic-like movements; in three instances, the authors observed CDV-free dogs presenting with seizures and myoclonic-like movements characterized by flexor spasms of the skeletal and facial muscles. Such dogs were diagnosed *post mortem* with non-suppurative meningoencephalitis (n=1) and Lafora´s disease – myoclonic epilepsy (n=2) [10]. In such cases the CDV-free condition was determined *post mortem* by RT-PCR in fresh CNS fragments.

3. Neurological presentations of CDV infection

The neurological signs depend on the CDV distribution in the CNS and localization of the lesions; however, a clinicopathological correlation may often be absent [10, 22, 33, 34]. *Post mortem* studies have diagnosed dogs presenting with focal signs; however, neuropathological evaluations detected diffuse multifocal lesions within all the neuroanatomical sites evaluated (cerebrum, cerebellum, brainstem, and spinal cord) [10]. In addition, dogs have also been observed to present with multifocal signs and focal lesions in only one neuroanatomical site [10].

With the use of RT-PCR and immunohistochemistry, the authors observed that independent of the signs and lesions, CDV infection is widespread within the CNS in dogs with nervous distemper. CDV may be observed to infect neurons and glial cells without histological changes on light microscopy [10].

Independent of the occurrence of neuropathological lesions, nervous infection by CDV may lead to a variety of neurological signs that may be recognized singly or in combination. CDV infection may lead to molecular dysfunction of the nervous cells at the level of neurotransmitters [35]; thus, molecular dysfunction could be responsible for some neurological signs found in dogs with distemper, even when corresponding lesions at the neuroanatomical site are absent [10].

4. Specific neurological dysfunctions of nervous distemper

In several studies involving naturally occurring nervous distemper, seizures and myoclonus were considered the most frequent neurological findings [20-22, 25-28, 36-38]. However, such clinical findings might result from a bias of selection, as the conventional signs of nervous distemper were considered as inclusion criteria.

Although seizure and myoclonus occur in CDV infection, they are not the primary clinical signs of nervous distemper. Distemper in immature dogs is the most common form of CDV infection and is characterized by convulsive disorders, often with myoclonus [39, 40]. However, such conventional presentation of CDV infection is not the rule. Mature dogs may be affected by distemper, and in such animals other non-convulsive nervous disorders may be prominent [11, 39, 41]. Although mature dogs presenting with conventional distemper-related encephalomyelitis may also present with myoclonus similarly to immature dogs [10], myoclonus is often absent in other presentations of nervous distemper in mature dogs such as *old dog encephalitis* and *multifocal distemper encephalomyelitis of mature dogs* [14, 32, 41, 42].

CDV affects both white and gray matter in the CNS. Thus, various neurological signs may be observed including behavioral changes, seizures, cerebellar and vestibular signs, visual deficits, paresis, paralysis, limb weakness, tremors, and myoclonus [9, 11, 12, 17, 30]. Seizure and myoclonus are typically gray matter signs, while visual deficits and different motor impairment are mainly signs of white matter dysfunctions [8].

Signs of leptomeningitis, such as cervical rigidity and generalized hyperesthesia, may also occur [8, 22]. Neurological signs may be acute or chronic; however, they are typically monophasic and progressive [7, 9, 11, 14, 30], although chronic relapsing nervous disease has been reported [43].

4.1 Myoclonus

Myoclonus is a gray matter sign characterized as a rhythmic jerking of single muscles or muscle groups [8]. Generalized or localized myoclonus has been observed in dogs with distemper encephalitis [20-22, 37, 38]. In some instances myoclonus may be confused with focal seizures, as flexor spasm of the limbs or twitching of facial muscles may occur in both myoclonus and focal seizures. Typically, in myoclonus the spasm is rhythmic, constant and present even during sleep.

Experimental studies have shown that focal spinal cord lesions may be responsible for this sign. It is speculated that the damage occurs in the lower motor neurons of the spinal cord or the cranial nerve nuclei. It is also possible that a basal nuclei lesion may initiate myoclonus by establishing a "pacemarker" in the cord or brainstem [44]. The mechanism of myoclonus in distemper is not well understood. In a clinicopathological study, no lesions in the gray matter of relevant spinal cord segments were found to account for the presence of myoclonus in 5 out of 13 spontaneous distemper cases with myoclonus [22].

4.2 Cerebral dysfunction and seizures

Cerebral dysfunction may be observed as seizures, compulsive walking, circling, head-pressing, and behavioral change. Such signs take place randomly in many combinations [7, 11]. Behavioral changes manifest as an increase in aggressiveness and disorientation as well as a loss of learned behavior. Circling due to cerebral dysfunction may occur in open or tight circles and may occur in both directions (to the left and to the right) in the same animal, although movement to only one side also may occur [10, 11].

Seizure is a gray matter sign [8] and may be focal/partial or generalized. Partial seizures are often followed by secondary generalization. Most partial seizures are characterized by twitching of the facial muscles [13]; however, focal contractions of the appendicular muscles (flexor movements) have also been observed [10]. Although the clinical signs of focal seizures depend on the part of the cerebrum that is affected, many focal seizures are described as "chewing-gum fits" [13, 45]. Generalized seizures are characterized by increased motor activity in all skeletal muscles (tonic-clonic or tonic movements), impairment of consciousness, and increased autonomic system activity (defecation, salivation, and micturition). Some convulsive dogs with distemper present at the hospital with neurological symptoms such as *status epilepticus* or clonus; these often die because distemper seizures may not be responsive to routine medical treatment [10].

4.3 Cerebellar and vestibular deficits

CDV has an apparent predilection for the cerebellopontine angle [10, 11, 22, 46], and cerebellar and vestibular deficits are frequently observed [11, 12, 39, 40]. These signs may be observed alone or in combination in the same animal [12, 22, 39]; however, combinations of signs are often observed [7, 10, 11].

Cerebellar and vestibular signs may be due to gray and/or white matter dysfunction. In the cerebellum, neuronal infection (Purkinje cells and granular neurons of the granular layer) and white matter demyelinating lesions might contribute to the manifestation of cerebellar signs [10]. Central vestibular signs may be due to dysfunctions of infected neurons in the vestibular nucleus or cerebellar neurons located in the nodulus and flocculus [10]. The nodulus and flocculus are regions of the cerebellum that play important roles in the vestibular system [47]. Vestibular signs may also be due to white matter lesions at the cerebellar peduncles, which connect the nodulus and flocculus in the cerebellum to the central vestibular nucleus in the brainstem [47, 48].

Cerebellar signs have been characterized by a lack of coordination of the head and trunk, tremors, ample base, dysmetria with hypermetry, and intentional tremor of the head or limbs [7]. Different cerebellar deficits may be recognized, but truncal and head ataxia with intentional tremor of the head are most often observed [11].

Although different cranial nerve deficits may be observed with nervous distemper [9, 12, 37, 40], the main cranial nerve sign is the dysfunction of the VIII cranial nerve (vestibulococlear nerve) [11]. The vestibular signs manifest as head tilt, positional or spontaneous nystagmus (horizontal, vertical, or rotatory), vestibular strabismus (positional strabismus typically occurring when the head is dorsally extended), and tendency to fall [7, 11]. Nystagmus and positional strabismus are the main vestibular signs of distemper [10, 11], and other typical vestibular signs, such as head tilt, are not frequent when compared to nystagmus and positional strabismus [10, 11]. Vestibular dysfunction may also be observed as conventional or paradoxical vestibular deficits (head tilting in the opposite direction from the side of the motor deficits, rapid movement of the nystagmus toward the side of the motor deficit) [10].

Neurological evidence suggests that vestibular deficits are central in all dogs with distemper; the main evidence includes vertical nystagmus, ventral positional strabismus, and the change in the direction of nystagmus with different positions of the head [10, 11]. Ventral positional strabismus (or vestibular strabismus) only occurs in central vestibular

disease [47]. Vertical nystagmus and the change of the nystagmus direction with different positions of the head are also associated with central rather than peripheral disease [40]. Curiously, nystagmus and vestibular strabismus have been observed with an episodic and relapsing nature in distemper dogs. In some dogs, these signs disappear during the clinical follow-up, and at the time of death such central vestibular signs may no longer be recognized despite the presence of severe neurological lesions in both the cerebellum and brainstem on *post mortem* evaluation [10].

In some dogs, although the neurological presentation is initially characterized by isolated cerebellar or vestibular signs, the association or overlap of such signs may occur during neurological evolution [10, 11]. Cerebellar and/or vestibular signs are often followed by progressive paresis, and the dogs become tetraparetic with disease evolution [11].

4.4 Ataxia

Different kinds of ataxia (proprioceptive, vestibular, and cerebellar) have also been recorded in distemper dogs. Ataxia is observed in most of the ambulatory dogs. Even in non-ambulatory tetraparetic patients, an initial history of motor incoordination (ataxia) is frequently reported by the owner. During the neurological examination of such cases, cerebellar and vestibular signs, as well as proprioceptive deficits, may be verified concurrently in the same animal. This observation suggests that all three mechanisms of ataxia (proprioception, vestibular, and cerebellar) may simultaneously contribute to the lack of motor coordination in dogs with distemper [10].

4.5 Circling in nervous distemper: a cerebral or vestibular sign?

Circling in nervous distemper is more common in dogs with cerebral dysfunction than in dogs with vestibular signs, even when tight circles are observed [10]. Tight circles alone may not be used to judge vestibular disease. Regardless of whether the circle is open or tight, in vestibular circling head tilt often occurs and other vestibular signs (nystagmus, vestibular strabismus, tendency to fall) may also occur. Tight circles in the absence of other vestibular dysfunctions may be a presentation of cerebral rather than vestibular lesions [49]. In addition, caution should be taken to not confuse adversion posture (head turning) due to unilateral cerebral dysfunction with head tilt [49]. Head tilt is characterized by deviation of the head (the line of the eyes are oblique) with or without nose deviation, and may be occasionally accompanied by head turning [49; 50]. With adversion posture, the head is turned (the nose is pulled around the flank) to one side; however, there is no deviation of the line of the eyes or ears (the observation of the eyes is more reliable than that of the ears) [49; 50; 51]. In cases of tight circling with adversion posture due to unilateral cerebral dysfunction, vestibular dysfunction might be misdiagnosed by a non-experienced clinician.

5. Final considerations

In summary, distemper has a broad spectrum of clinical courses and neurological signs. Thus, the clinical diagnosis of nervous distemper may be difficult because many other CNS dysfunctions may lead to similar presentations. Occasionally, the diagnosis of distemper may be a challenge for the veterinarian; however, in areas where CDV is endemic, such as Brazil, distemper should be always considered as an important differential diagnosis in dogs with progressive and multifocal neurological disease. Even in focal nervous dysfunction, CDV infection should be investigated.

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