FULL PAPER *Pathology*

Clinicopathological Features of Canine Neuroaxonal Dystrophy and Cerebellar Cortical Abiotrophy in Papillon and Papillon-related Dogs

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(Received 17 April 2007/Accepted 21 June 2007)

ABSTRACT. Neuroaxonal dystrophy (NAD) was examined in two Papillon dogs and a mix breed dog between Papillon and Chihuahua. In addition, cerebellar cortical abiotrophy (CCA) in a Papillon dog, which had similar clinical and magnetic resonance imaging (MRI) features to those of NAD, was also investigated. The common clinical symptoms of all dogs affected with NAD and CCA, were pelvic limb ataxia and cerebellar ataxia including intention tremor, head tremor, and hypermetria in the early onset. These clinical signs were progressed rapidly, and two dogs with NAD were euthanized by owner's request and the other two were died by aspiration pneumonia. MRI examinations and gross observations at necropsy revealed moderate to severe cerebellar atrophy in all cases of NAD and CCA. The most typical histological change of NAD was severe axonal degeneration with marked spheroid-formation in the dorsal horn of the spinal cords, the nuclei gracilis, cuneatus, olivalis and its circumference in the medulla oblongata. The spheroids were characterized as large eosinophilic or granular globes within the enlarged myelin sheaths, sometimes accompanied by moderate accumulation of microglias and/or macrophages. In contrast, such spheroid formation was minimal in the brain of CCA. In the cerebellum, mild to moderate loss of the Purkinje and granular cells were recognized in three dogs with NAD, whereas these changes were more prominent in a dog with CCA. Although the clinical signs and MRI findings relatively resembled between NAD and CCA, the histopathological features considered to be quite differ, suggesting distinct pathogenesis and etiology. Since both NAD and CCA are proposed as the autosomal recessive hereditary disorders, careful considerations might be needed for the breeding of Papillon and Chihuahua dogs.

KEY WORDS: canine, cerebellar abiotrophy, neuroaxonal dystrophy, Papillon, spheroid.

J. Vet. Med. Sci. 69(10): 1047–1052, 2007

Neuroaxonal dystrophy (NAD) is a group of neurodegenerative disorders characterized by severe degeneration of neuronal cells and their processes resulting in prominent spheroid formation in the central nervous system. However, these morphological changes are observed not only in NAD but also in several neurodegenerative disorders such as abiotrophy and lysosomal storage diseases [13, 19, 25]. By Sacre *et al.* [22], NAD was defined as an incidental age-related finding which associates with various spontaneous and experimental diseases, such as exposure to toxins and deficiency states. In addition, NAD had a characteristic lesion of a group of degenerative diseases [22]. Spontaneous cases of NAD have been reported in dogs [2, 5, 6, 8, 9, 22, 24, 25], cats [4, 20, 21, 25], horses [25], sheep [25], and humans [11, 12, 15, 17]. Recently, a mouse model of NAD identified as a spontaneous mutation in a BALB/c congenic mouse strain has been also described [3].

As possible etiology of NAD, various factors, such as vitamin E deficiency, exposure to toxins, and some genetic alterations have been suspected [5, 18]. Among them, genetic factor is most likely for the major cause of NAD in domestic animals and humans. Several reports concerning NAD in domestic animals suggested that NAD might be an autosomal recessive disorder. In canine NAD, Rottweiler is known as the predisposed breed. In other canine breeds, NAD has been reported in Papillion [9], Jack Russell terrier [22], and collie sheep dog [6]. Moreover, similar disorder to NAD has been also reported in a Chihuahua designated as "axonal swelling" [2]. In most hereditary NAD in domestic animals, the typical clinical symptoms include cerebellar ataxia, such as incoordination of the limbs, hypermetria, and an intention tremor, and the clinical onset appears at quite young age with raid progressive course. The pathological lesions are usually found widely in the central nerves system, and those are remarkable at the dorsal horn of the spinal cords, nuclei gracilis, cuneatus, and olivalis of the medulla oblongata.

On the other hand, abiotrophy is one of the concepts of neurodegenerative disease in veterinary field [1, 17, 23], while is no more used in human medicine. The neurological term represents as a lack of a life-sustaining nutritive factor in literally, and results from spontaneous, premature and progressive neuronal degeneration and death [25]. Previously, de Lahunta [7] defined all the neurodegenerative disorders as abiotrophy, except for lysosomal storage diseases and leukodystrophies [7]. Among them, cerebellar cortical abiotrophy (CCA) has been most frequently developed in dogs [7]. Canine CCA is considered to be autosomal recessive as well as NAD, and detailed researches have been performed on the cases in Kerry blue terrier [25]. Major

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clinical sings of CCA are cerebellar ataxia including head tremor, truncal ataxia, symmetrical hypermetria, spasticity, broad-based stance, and the loss of balance. Pathologically, the primary loss of the Purkinje cell and the secondary loss of the granule cells is a unique nature of CCA. Thus, NAD and CCA have relatively overlapped clinicopathological features.

The present study describes the clinical and pathological features of canine NAD in two Papillion and a mix breed between Papillion and Chihuahua, together with CCA in a Papillion. The similarity and differences of these two canine neurodegenerative disorders and possible etiologies are discussed.

MATERIALS AND METHODS

Case histories: Three cases of NAD (dog 1 to 3) and a case of CCA (dog 4) are available for this study. The cases investigated were 3 Papillon dogs (dog 2, 3 and 4) and a mixed breed between Papillon and Chihuahua (dog 1). The clinical features of these dogs examined are summarized in Table 1. There were no familial relationship among these 4 cases examined, and no records concerning the status of their littermates.

Histopathology: The cerebrum, cerebellum, medulla oblongata, and spinal cords from 4 affected dogs were used for the examination. Normal brain tissues of a Papillon were used as a control for histology and immunohistochemistry. Major visceral organs from 2 affected dogs were also available for examination. The tissue samples were fixed with 10% formalin. Paraffin sections of 6 μm thick were prepared and stained with hematoxylin and eosin (HE). Some selected sections were stained with Klüver-Barrera (Luxol Fast Blue). Immunohistochemistry was performed using Envision polymer reagent (DAKO-Japan, Kyoto, Japan). The primary antibodies were monoclonal antibodies against canine distemper virus (1:100, CDV-NP MAb, VMRD Inc., Pullman, WA, U.S.A.), phospholylated and non-phospholylated neurofilament (1:250, Chemicon International Inc., Temecula, CA., U.S.A.), and HLA-DR (1:25, Dako-Japan), and rabbit antiserum against glial fibrillary acidic protein (GFAP; Prediluted, Dako-Japan).

Quantitative analysis: Purkinje cells were counted in randomly selected 10 fields of the cerebellar vermis and hemisphere in magnification of $\times$ 400. Spheroids more than 5 μm in diameter were counted in randomly selected 5 fields of the dorsal horn of the spinal cords and nuclei gracilis, cuneatus, and olivalis of the medulla oblongata in magnification of $\times$ 400.

RESULTS

Clinical findings: Dog 1 (Papillon $\times$ Chihuahua, male, NAD) exhibited pelvic limb ataxia with broad-based stance and cerebellar ataxia including intention tremor and hypermetria at 3 months old of age. These clinical symptoms advanced for 2 months, and then additional signs of myotonia and ananastasia were appeared. Neurological examinations revealed loss of conscious proprioception. Blindness, deafness, anosmia, and lost of the swallowing reflex indicating the brain stem abnormalities appeared at 7 months old. Then, the dog had difficulty for eating at 8 months old and was euthanized by owner's request.

Dog 2 (Papillon, female, NAD) exhibited progressive pelvic limb ataxia with ananastasia and cerebellar ataxia including head tremor, at 4 months old. Neurological examinations revealed the loss of a posture reaction and menace reflex. At 5 months old of age, tetraplegia and tongue paralysis were added to the clinical symptoms. By neurological examinations, the loss of knee jerk reflex and abnormalities in the femoral nerve were accepted, but deep pain was intact. The dog was euthanized by owner's request at 6 months old of her age.

Dog 3 (Papillon, female, NAD) showed pelvic limb ataxia, cerebellar ataxia including intention tremor, hypermetria of former limb, and head tremor at 3 months old. The neurological examination revealed no abnormality of light reflex, the functions of the trigeminal nerves and facial nerve, spinal reflex, and acrognosis. No nystagmus was observed. The ananastasia of the hind foot and head tremor appeared at four months. In addition, paralysis of the whole body except for the function of the jaw and expansion of all

Table 1. Summary of clinical information of cases

		Breed	Gender	Onset	Death	Major clinical signs
NAD	Dog 1	Papillon $\times$ Chihuahua	♂	3m	8m*	intension tremor, hypermetria, pelvic limb ataxia, myotonia, visual deficit, blindness, deafness, anosmia
	Dog 2	Papillon	♀	4m	6m*	head tremor, intension tremor, pelvic limb ataxia, tongue paralysis, tetraplegia
	Dog 3	Papillon	♀	3m	9m	intension tremor, head tremor, hypermetria, pelvic limb ataxia, ananastasia
CCA	Dog 4	Papillon	♂	6m	2y10m	broad-based stance, pelvic limb ataia, truncal ataxia, head tremor, intension tremor, loss of menace response, upper motor neuron sign, facial nerve paralysis

*: euthanatized by owner's request.

limbs were observed. The dog died by aspiration pneumonia at 9 months old of her age.

Dog 4 (Papillon, male, CCA) showed broad-based stance with pelvic limbs and truncal ataxia at 5 months old, and then progressed slowly. The physical examinations revealed head and truncal ataxia, head tremor with intension tremor, and loss of menace response. The laboratory examinations revealed no abnormalities. Then, the puppy had showed upper motor neuron signs consisting of pelvic limb spasticity. At one year and six months of his age, the dog exhibited general paresis, and then was unable to stand at 2 years of age. At 2 years and 9 months of age, the dog had difficulty for swallowing and left facial nerve paralysis, indicating the disorders of the brain stem and died by aspiration pneumonia.

By MRI examinations, moderate to severe atrophy of the cerebellum was observed in all dogs examined. Gross observations of formalin-fixed brains also revealed moderate to severe cerebellar atrophy in all cases (Figs. 1 and 2).

Histopathological findings: The histological features commonly found in NAD dogs (dogs 1 to 3) were moderate to severe axonal degeneration characterized by spheroid formation or swollen neuritis/axons in the central nervous system (Fig. 3), while these axonal changes were less prominent in dog 4 diagnosed as CCA. Although these axonal changes were widely distributed throughout the central nerve tissues in NAD dogs, the lesions were tended to localize dominantly in the spinal dorsal horn, nuclei gracilis, cuneatus, lemniscus medialis, and nuclei of the spinal tract of the trigeminal nerve, lemniscus trigeminalis, olivalis, and its circumference in the medulla oblongata. The neuronal cells in these regions with numerous spheroids were well preserved, while some exhibited ischemic changes. The axonal spheroids were varied in size, ranging from approximately 5 to 50 μm in diameter, round to oval in shape, and homogeneously eosinophilic or granular in appearance (Fig. 4). Some myelin sheaths with spheroids exhibited mild to moderate dilation, although KB stain revealed that myelin were relatively preserved. In the regions with severe axonal degeneration, mild to moderate proliferation of HLA-DR-positive microglias and/or macrophages was found diffusely in the neuropile and occasionally within the vacuolated myelin sheaths. Infiltrations of inflammatory cells other than macrophages were less prominent in any brain regions of all NAD dogs. Immunostaining for GFAP revealed moderate proliferation of GFAP-positive astrocytes in several regions with numerous spheroids.

In addition to the prominent spheroid formation, degenerative lesions of the cerebellum characterized by mild to moderate loss of Purkinje and granular cells with astrocytosis, were found in 3 dogs with NAD (Fig. 5). Moreover, the nucleus of granular cells of dog 3 (NAD) and dog 4 (CCA) were pyknotic in appearance. In the granular cell layer and white matter of the cerebellum, there were small number of swollen axons called as "torpedoes" and moderate astrocytosis. As compared to the cerebellar lesions of CCA dog, the degree of Purkinje and granular cell-loss was milder in those of NAD dogs, while spheroid or torpedo formation was less prominent in the cerebellum of CCA dog. Especially, the degree of granular cell-loss in CCA was more severe than those in NAD dogs (Fig. 6). The severity of Purkinje cell-loss was differ in each location of the cerebellum and was most prominent in the vermis in both NAD and CCA dogs. The number of Purkinje cells of NAD dogs 1 to 3 were 2.5 ± 1.3, 2.4 ± 1.3, and 2.2 ± 1.5, respectively. The mean number of the affected cases was less half than the number of normal control (6.1 ± 1.3). In CCA dog, the number of Purkinje cells was 0.8 ± 0.87 which was less one sixth than the normal control (Table 2).

The schematic anatomical regions and their connections with severe pathological lesions of three NAD dogs examined are representing in Fig. 7. In contrast to NAD, histopathological changes of CCA are mostly restricted in the cerebellar cortex.

In the visceral organs without the nervous tissues in dog 2, the liver, spleen, and adrenal gland were pathologically intact. Almost all systemic organs in dog 3 were also normal. Immunohistochemically, no viral antigens for canine distemper virus were detected in any organs including nervous tissues.

DISCUSSION

Three cases, dog 1 to 3, diagnosed as NAD had similar clinical and pathological findings, which were almost consistent with those of previously described canine NAD. Peculiar clinical symptoms and histopathological change in NAD are quite important to diagnose and to discriminate from other degenerative disorders. The onset of clinical signs including pelvic limb ataxia and cerebellar ataxia, were observed until 6 months old of age in all NAD cases. The rapid progress of the clinical signs was common event and all NAD dogs were difficult to sustain their life until one year. Histopathologically, the disease was characterized by widely spread nerve fiber degeneration representing as spheroids formation predominantly localized in the sensory tracts. The distribution pattern of the lesions seems to reflect clinical signs in the present NAD cases. Those dorsal horn, nuclei gracilis, cuneatus, lemniscus medialis, and thalamus constitute medial lemniscus system are the tracts to transmit the esthesia of limbs and trunk. The loss of spinal reflexes including knee jerk reflex of dogs 2 and 3 might be associated to the damage of this tract. The nucleus spinalis nervi trigemini, lemniscus trigeminalis and thalamus constitute trigeminal system are the tracts to transmit mainly esthesia of head. The tongue paralysis of dog 2 and the lost of the swallowing reflex of dog 1 might reflect the damage of trigeminal system. Furthermore, the nuclei olivalis and cerebellum constitute olivocerebellar tract are the relay tracts between the spinal cord and cerebellum.

Besides, the clinical features of CCA are quite similar to those of NAD dogs. As de Lahanta [7] has previously classified NAD into the abiotrophy, the certain distinction of these diseases during lifetime by clinical signs, neurological

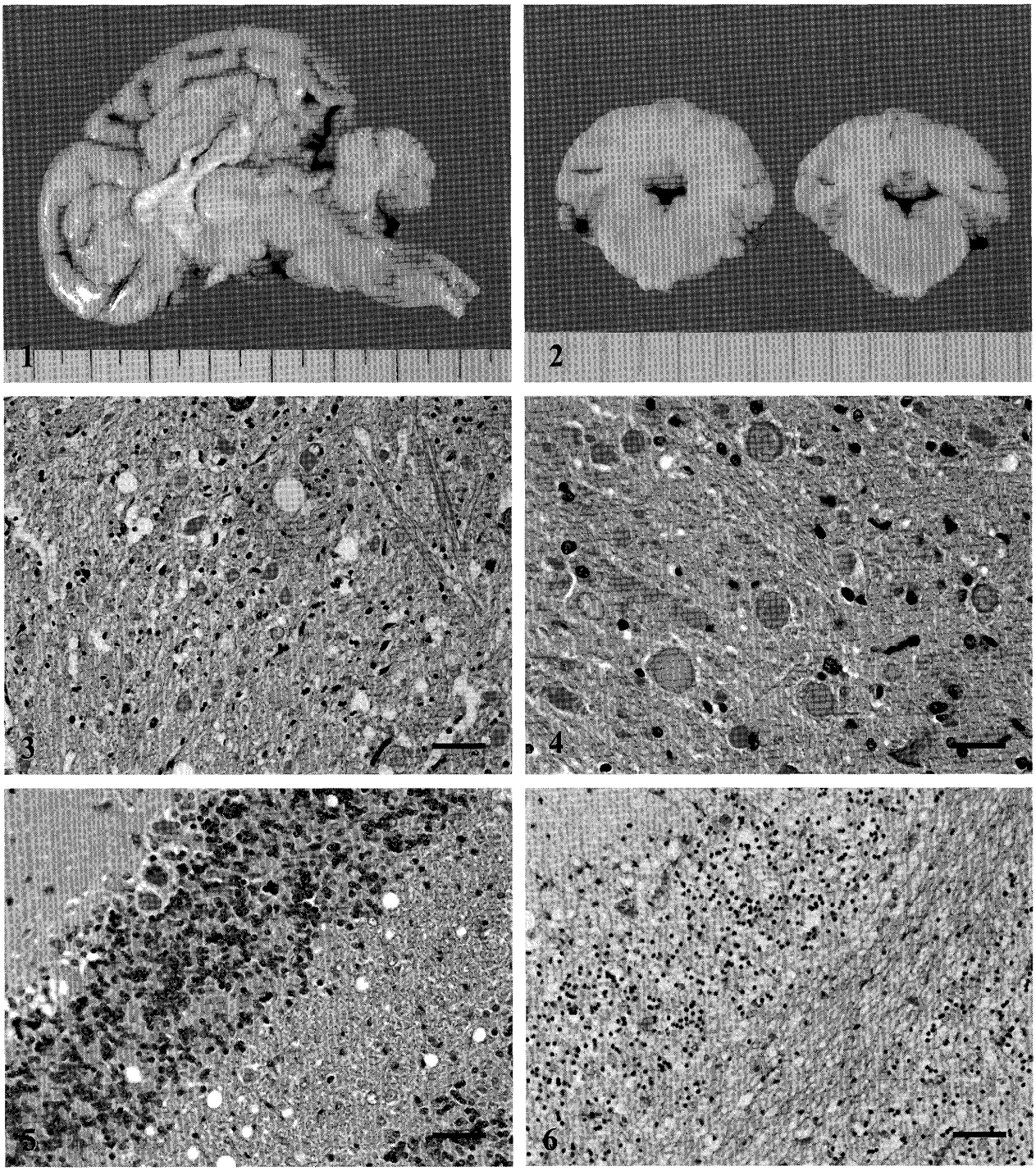

Fig. 1. Dog 1. Gross lesion of the brain at sagittal plane. Moderate to severe atrophic appearance of the cerebellum is observed.
Fig. 2. Dog 2. Gross lesion of the cerebellum and medulla oblongata at transverse sections. Moderate to severe atrophic lesion of the cerebellar cortex.
Fig. 3. Dog 3. Dorsal horn of the spinal cord. There are a quite number of spheroids varied in size and moderate proliferation of glial cells. HE stain. Bar=100 μm.
Fig. 4. Dog 2. Olivalis nucleus. The spheroids are eosinophilic homogeneity, granular to floccular, and target-like in texture. HE stain. Bar=50 μm.
Fig. 5. Dog 2. Cerebellar vermis. Histopathological appearance of the cerebellar cortex of NAD. There is mild loss of Purkinje cells, while granular cells are relatively preserved. HE stain. Bar= 100 μm.
Fig. 6. Dog 4. Histopathological appearance of the cerebellar cortex of CCA. There was severe loss of both Purkinje and granular cells. The granular cells were pyknotic in appearance. HE stain. Bar=100 μm.

Table 2. Number of survived Purkinje cell

		Cerebellar vermis	Cerebellar hemispher
Normal		6.1 ± 1.3	–
NAD	Dog 1	2.5 ± 1.3	2.4 ± 0.66
	Dog 2	2.4 ± 1.3	4.7 ± 1.0
	Dog 3	2.2 ± 1.5	4.5 ± 1.0
CCA	Dog 4	0.8 ± 0.87	1.2 ± 0.98

It shows the number of survival Purkinje cells in cerebellum of NAD and CCA.

examinations, and/or diagnostic imagings may be difficult. The progress speed of the clinical signs and survival period might be discriminatable points between NAD and CCA because all cases of NAD dogs investigate in this study died under 1 year old, while CCA dog could survive for about 3 years. The pathogenesis of CCA, as well as NAD, has not been well elucidated. In dogs, Kerry blue terrier was reported as predisposed breed for CCA and previous epidemiological studies indicated the possibility of hereditary etiology by autosomal ressive manner [24, 25].

Some human NAD is occurred by accumulation of iron in the brain [11, 12, 15, 17]. On the other hand, spinocerebellar degeneration type6 is caused by expansion of CAG repeat in the coding region of CACNA1A corresponding to a P/Q type voltage-gated Ca^{2+} channel [10, 14, 16]. Interestingly, Groggy rats with point mutation of the P/Q type voltage-gated Ca^{2+} channel [26, 27, 28] is thought to have some histological similarity with canine NAD. Similar genetic alterations of an essential gene for a group of neuronal cells might be possible for the etiology of canine NAD or CCA.

In conclusion, the present paper indicated the clinicopathological features of NAD and CCA in Papillon and mix breed dog between Papillon and Chihuahua. It is supposed that Papillon and probably Chihuahua pedigrees in Japan have possibly some genetic factors for these neurodegenerative diseases. Therefore, careful considerations are recommended for the breeding of these dogs. Further specific studies to know the natures of spheroids in NAD dogs and molecular biological investigations will be needed to elucidate the pathogenesis of canine NAD and CCA.

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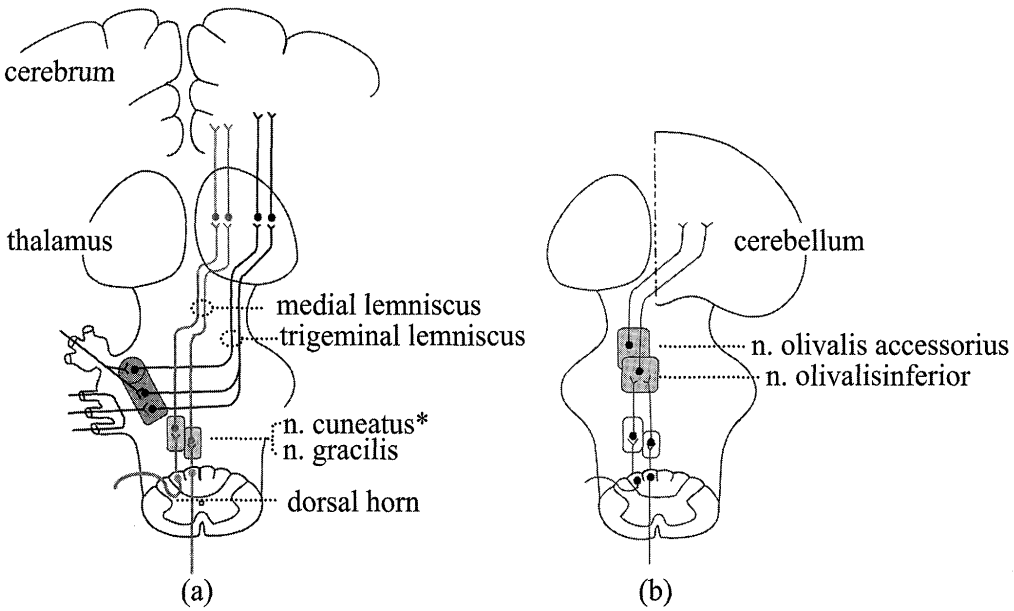

Fig. 7. Schematic anatomical regions and their connections with severe pathological lesions of 3 NAD dogs (dog 1 to 3). (a):dorsal horn, nucleus cuneatus and gracilis and thalamus of medial lemniscus system (gray space and line). Nucleus spinalis nervi trigemini of trigeminal system (dark gray space and black lines). (b) Nucleus. olivalis accessorius and nucleus. olivalisinferior of olivocerebellar tract. * n: nucleus.

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