Hereditary necrotising myelopathy in Kooiker dogs

P. J. J. MANDIGERS, Department of Pathology, J. J. VAN NES, B. W. KNOL, G. J. UBBINK, Department of Clinical Sciences of Companion Animals, E. GRUYS, Department of Pathology, Faculty of Veterinary Medicine, University of Utrecht, Yalelaan 1, 3508 TD Utrecht, The Netherlands

A retrospective clinicopathological study of a neurological disorder in 22 Kooiker dogs (Dutch decoy dog) was made. The disease was found to occur equally in both sexes and clinical signs began at three to 12 months old. Physical examination revealed a progressive paresis of the hindlimbs. Postmortem examination showed symmetrical areas of ataxia in the ventral, lateral, and dorsal white matter of the spinal cord. In one dog dorsal white matter was spared. Cervical segments C4 to C8 were involved in all subjects. Rostral and caudal to these areas, Wallerian degeneration was prominent. The disease has much in common with similar myelopathies in the Afghan hound and the rottweiler. Indications of heritability were the similarity in clinical and pathological findings, the age of onset of the disease, and the significantly higher inbreeding coefficient in the patients than in the breed population (P<0.001). All patients were descended from one pair. Segregation analysis suggested inheritance involving a simple autosomal recessive trait.

THE Kooiker dog is an old Dutch breed originally used to catch ducks in a decoy (Fédération Cynologique Internationale registration number 354). The animal was used to attract swimming wild ducks to a special canal "pipe-tap" where they could be captured by hand. After the Second World War only 30 of these dogs remained. These 30 animals, and 10 of them in particular, were used to re-establish the breed (P. J. J. Mandigers, unpublished data). Since 1962 young Kooiker dogs have been presented with ataxia, paresis, and paralysis. The signs started in the hindlimbs and progressed to tetraparesis and paralysis. Postmortem examination revealed a symmetrical bilateral necrotising myelopathy with malacia in the ventral and dorsal white matter. The disease resembled the hereditary myelopathy seen in Afghan hounds (Cummings and de Lahunta 1978) and the leukoencephalomalacia in rottweilers (Gamble and Chrusanne 1984, Wouda and Van Nos 1986). Familial spinal cord abnormalities described in several other breeds of dogs have been reviewed by de Lahunta (1983) and by Longhofer et al (1990). In most other breeds a genetic cause has been suspected or demonstrated (Averyll and Bronson 1977, Braun and Vendevelde 1978, Vandevelde 1988, Bichsel et al 1983, Wouda and Van Nos 1986).

In this report the clinical, pathological, and pedigree data on 22 Kooiker dogs are presented with the conclusion that they had a familial necrotising myelopathy. Segregation analysis suggested that the disease is hereditary and involves a simple autosomal recessive trait.

Materials and methods
Population and patients
From 1962 to 1990, 46 young Kooiker dogs were found to have clinical signs of posterior paresis and ataxia. Twenty-two dogs (10 males and 12 females) were available for a retrospective study. The 22 subjects were derived from 12 litters with a total of 55 littermates (including the subjects). Thirteen of the subjects were examined at the Department of Clinical Sciences of Companion Animals, and nine by local veterinarians. Fourteen of the subjects, of which 12 were examined at the university clinic, were available for pathological examination. There was no specific geographical distribution. The purebred Kooiker dog population born between 1942 and 1990 consists of 4927 animals.
Clinical and pathological examination

All 22 dogs were adequately vaccinated against canine distemper and infectious canine hepatitis. General physical and neurological examinations as well as routine haematological and blood chemistry examinations were carried out. The spinal column was X-rayed. The dogs were euthanised with an overdose of barbiturate. At post-mortem examination the brain and spinal cord, and samples of various other tissues, were fixed in 4 per cent buffered formaldehyde. Paraffin-embedded sections were stained with haematoxylin and eosin. Special stains used on central nervous system tissues were haematoxylin fast blue-Cresyl echt violet, periodic acid-Schiff (PAS), toluidine blue, and Weil's, Weigert's and Holzer's staining methods.

Pedigree analysis

The pedigrees of all 22 dogs were analysed. Pedigree data for the complete population from 1942 to 1990 (n=4927) were kindly provided by the Association of the Dutch Kooiker Dog. The inbreeding coefficient was calculated beginning with the first 30 dogs which were used to re-establish the breed. The calculations were performed by computer, using Wright's inbreeding coefficient (Wright 1922). The complete population (n=4574) living during the same period (1962 to 1990) as the 22 subjects was used as the reference group. Since inbreeding coefficients in populations are not normally distributed, the non-parametric two-rank sample test of Wilcoxon was used (Mann and Whitney was used for statistical analysis (Armitage and Berry 1988).

No clinical data were available from three pure-bred dogs and therefore two litters (six subjects) were excluded from segregation analysis. Only parent dogs having no locomotory problems or ataxia at the time of death (eight years old or more) were considered to be clinically unaffected and therefore carriers. A segregation analysis was performed by counts of the remaining 16 patients versus the total count of remaining littermates (n=46). When both parents were carriers (simple Mendelian inheritance) the expected segregation was one in four littermates affected. For autosomal inheritance both sexes must be equally affected. These hypotheses were tested using a \( \chi^2 \) test.

Results

Clinical findings

All animals had a history of progressive abnormalities in locomotion, starting in the hindlimbs when they were between three and 12 months old. The 13 dogs examined at the university clinic had mild to severe ataxia and ataxia in the hindlimbs. In five of the 13 dogs the forelimbs were also affected. In nine the spinal reflexes were exaggerated, and in six there were abnormalities in proprioceptive perception. Six dogs had a distended bladder with a high resistance to expulsion of urine. No other physical abnormalities were found.

Routine blood examination revealed no abnormalities. Radiographs of the spinal columns of 12 dogs available for examination revealed no evidenz lesions. Myelography in one of these dogs showed no abnormalities.

The period from the onset of clinical signs to euthanasia ranged from two weeks to 11 months (median two months). The age at death ranged from five to 20 months (median 12 months).

Pathological findings

Gross and histological abnormalities were confined to the central nervous system. In all 14 dogs cross sections of the fixed spinal cord showed transparent areas. In stained sections these lesions were distributed more or less symmetrically in the white matter and showed a marked deficiency of staineable myelin and of axons (Fig 1). In all subjects, lesions were most prominent in the first cervical and first thoracic segments and were localised primarily in the ventral and dorsal columns. The ventral malacic areas extended to involve lateral columns in some cervical and, or, thoracic segments of most patients. In one dog all white matter was involved in some thoracic segments (the dog in group V of Fig 2). On the basis of histological patterns, the dogs were divided into five groups but these did not correspond with the duration of the disease (Fig 2).

The necrotic areas of the cervical, thoracic and lumbar segments of the cord were characterised by complete loss of white matter, especially in the centre of the dorsal and ventral white columns (Fig 2). A superfical rim was spared around most necrotic foci (Fig 1). Reactive vascular prolifer-
FIG 1: Dog 3 (group III, C7). Ventral central white matter. Note the non-staining area with demyelination. A superficial small rim of white matter is spared (arrow). Luxol fast blue-Cresyl violet × 18

FIG 4: Dog 10 (group II), T2. Malignant area in ventral white matter. Blood vessels surrounded by connective tissue. The original tissue is replaced by xanthophages. Haematoxylin and eosin × 100

FIG 2: Schematic representation of the various observed patterns of lesion distribution in the spinal cord of the 14 neoplastic Kooler dogs. Black stained areas represent malacic, dotted regions Wallerian degeneration

FIG 5: Dog 1 (group I), C7. Serosed neuron (arrow) within an oedematous demyelinated area. Luxol fast blue-Cresyl violet × 200

FIG 3: Dog 3 (group III, C7). Ventral white matter. Note the vascular reaction (white) in malacic central part of demyelinated area. Holzer × 10

Degeneration was predominant (Fig 3), often surrounded by masses of macrophages (Fig 4). There were some gemistocytic astrocytes. Some lesions progressed to liquefactive necrosis with gitter cells. At the border of the necrotic areas, axons were still present, although myelin was lost. Wallerian degeneration was prominent in spinal cord segments caudal to the ventral and lateral areas of malacia and cranial to the dorsal areas of malacia. Spinal cord neurons and nerve roots were generally unaffected. In 10 dogs the necrotic white matter extended to the ventral grey matter, but in the four other animals ventral grey matter was also involved, neurons being surrounded by degenerated tissue and macrophages, although the neurons appeared to be intact (Fig 5).
With regard to involvement of the brain, in some dogs the dorsal spinal fascicular Wallerian degeneration extended to the gracilis and cuneatus nuclei. In three dogs slight (one in group I and one in group JJ, Fig 2) or heavy (in one of group IV, Fig 2) degeneration of the trapezoid corpus was found. In two other dogs some vacuolation within the olivary nuclei occurred.

Pedigree analysis

Attempts to re-establish the breed had resulted in high levels of inbreeding. The level of inbreeding of the reference group (n=4754) varied from 0.0000 to 0.475, with a median of 0.1465. The level of inbreeding of the patients (n=22) varied from 0.1277 to 0.3592, with a median of 0.2296.
These levels of inbreeding differ significantly (P<0.001). The general population were descend-
ded from 30 dogs, while all the affected dogs were descended from one pair and only four in all of the original 26 dogs (Fig 6).

No clinical data were available for three of the parents of these 22 puppies and therefore the two litters had to be excluded (Fig 6). The remaining litters comprised 10 affected females and six unaffected males but this gender difference was not significant (P>0.05). Using the hypothesis that both parents were carriers, the expected segre-
gation of the remaining litters would be 11:5 affected out of 46 animals. The difference from the actual 16 out of 46 was not significant (P>0.05), suggesting a simple autosomal/recessive mode of inheritance.

Discussion

The first three cases of "Kooikerparalyse" were mentioned in a clinical lecture by Verwey (1968). He described degeneration of dorsal and ventral spinal tracts in three young Kooiker dogs, which are included in the present series.

Clinical and pathological findings were similar in all the cases described here. The results of neurological examination confirmed a multifocal disorder of the cervical spinal cord or a diffuse disorder of the spinal cord (Wheeler 1989). The preservation of axons as the border of the necrotic lesions in the white matter in the 14 necropsied dogs suggests primary demyelination. It is rea-
sonable to relate the apparent neurological deficits to the necrotic and Wallerian lesions in the ascending as well as descending fibre tracts (Rasmovsky 1980).

The clinical and pathological findings have much in common with those of hereditary myelopathy in Afghan hounds (Cummings and de Lahouta 1978) and leucoscelalphoamelato-
pathy in rottweilers (Gamble and Chishnitz 1984, Wouda and Van Nes 1996).

Afghan myelopathy causes ataxia and rapidly progressive paralysis. The lesions, mainly located in the lower cervical and mid-thoracic spinal cord, consist of myelinolysis and malaeria rather than dysmyelino genesis, and have been compared with myelinopathies of toxic/metallic origin (Cummings and de Lahouta 1978).

in rottweiler leucoscelalphomoamelopathly, older animals (1.5 to 3.5 years) develop a slowly pro-
gressive ataxia and paraparesis. Symmetrical lesions have been found in the spinal cord, brainstem and cerebellum. Both demyelination and remyelina-
tion have been observed (Wouda and Van Nes 1980). Gamble and Chishnitz (1984) suggested a vitamin B12 deficiency. A myelopathy associ-
ated with vitamin B12 deficiency is known in sheep (van den Broeck 1984) and in the horse of vertebral cord and to affect all function (Adams and Sidman 1968). In English foxhounds and barrier, diffuse degener-
ation of white matter was described as being associated with vitamin B12 deficiency caused by feeding high-starch starchy diets (Sheahan et al 1991). In the Kooiker dogs the lesions were more localised.

The clinical and pathological findings in these 22 pure bred Kooiker dogs suggest a leucomyo-
trophic type of disease. The mode of inheritance has often founds in leucodystrophy is simple Meneliear inheritance (Crome and Stern, 1976). There are strong indications of heritability includ-
ing the similarity in clinical and pathological findings, the age of onset of the disease, and the higher levels of inbreeding in the 22 affected dogs (Patterson et al 1989). The fact that both sexes were affected and had clinically normal parents is compatible with an autosomal mode of inher-
tance. Segregation analysis confirmed this hypothesis.

The Kooiker dog population consists of 2500 animals living in the Netherlands. The breed is popular and the population is growing steadily, and therefore prone to genetic disease (Willa 1989). The observed symmetry, primary demyeli-
nation and the apparent heritability in Kooiker dogs as well as in Afghan hounds and rottweilers are strong reasons for classifying all of these neo-
rological disorders as leucodystrophic diseases.

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References


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