Research in Veterinary Science 1993, 54, 118-123

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. Post mortem examination showed symmetrical areas of malacia 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 Cynologic International registration number 314). The animal was used to attract swimming wild ducks to a special canal 'pipe-trap' 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 These 30 animals, and 10 of them in particular, were used to re-establish the breed (P. J. J. Mandigers, unpublished data).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. Post mortem 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 leucoencephalomyelopathy in rottweilers (Gamble and Chrisman 1984, Wouda and Van Nes 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 (Averill and Bronson 1977, Braund and Vendevelde 1978, Vandevelde 1980, Bichsel et al 1983, Wouda and Van Nes 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 euthanased 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 luxol fast blue-Cresylecht 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, Mann and Whitney was used for statistical analysis (Armitage and Berry 1988).

No clinical data were available from three parent 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 χ^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 paresis 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 evident 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 stainable myelin and of axons (Fig 1). In all subjects, lesions were most prominent in the last 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 superficial rim was spared around most necrotic foci (Fig 1). Reactive vascular prolifer-

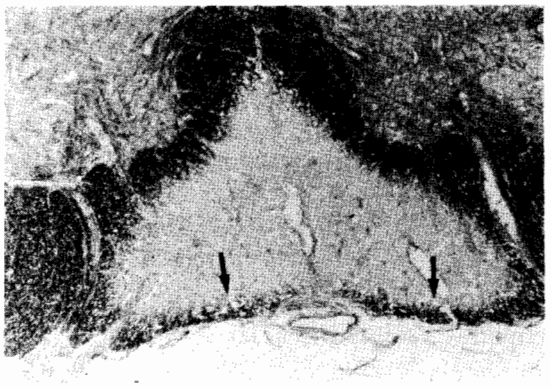

FIG 1: Dog 5 (group II), C7. Ventral central white matter. Note the non-staining area with demyelination. A superficial small rim of white matter is spared (arrow). Luxol fast blue-Cresylecht violet × 18

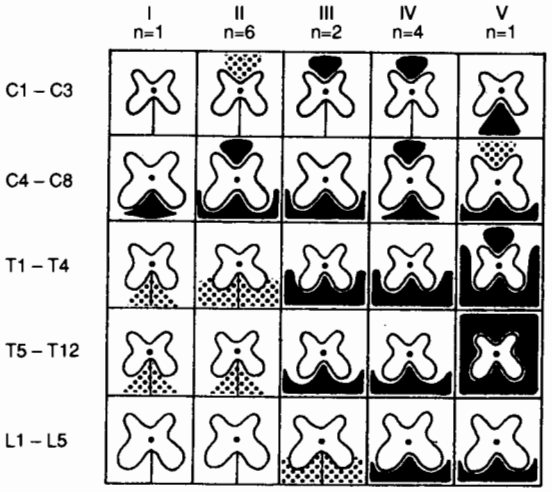

FIG 2: Schematic representation of the various observed patterns of lesion distribution in the spinal cord of the 14 necropsied Kooiker dogs. Black stained areas represent malacia, dotted regions Wallerian degeneration

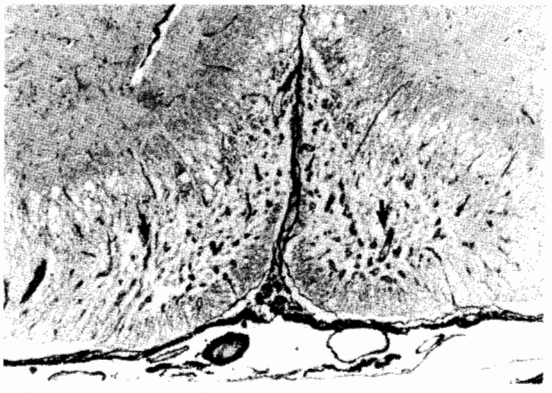

FIG 3: Dog 8 (group III), C7. Ventral white matter. Note the vascular reaction (arrow) in malacic central part of demyelinated area. Holzer × 18

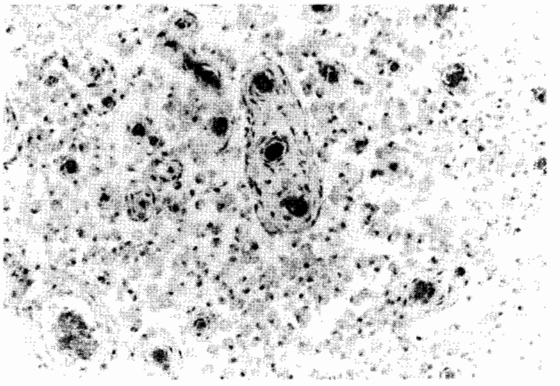

FIG 4: Dog 10 (group II), T2. Malacic area in ventral white matter. Blood vessels surrounded by connective tissue. The original tissue is replaced by macrophages. Haematoxylin and eosin × 100

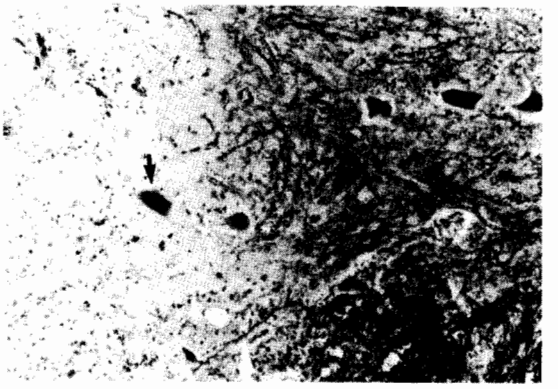

FIG 5: Dog 1 (group I), C7. Spared neuron (arrow) within an oedematous discoloured demyelinated area. Luxol fast blue-Cresylecht violet × 200

ation 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).

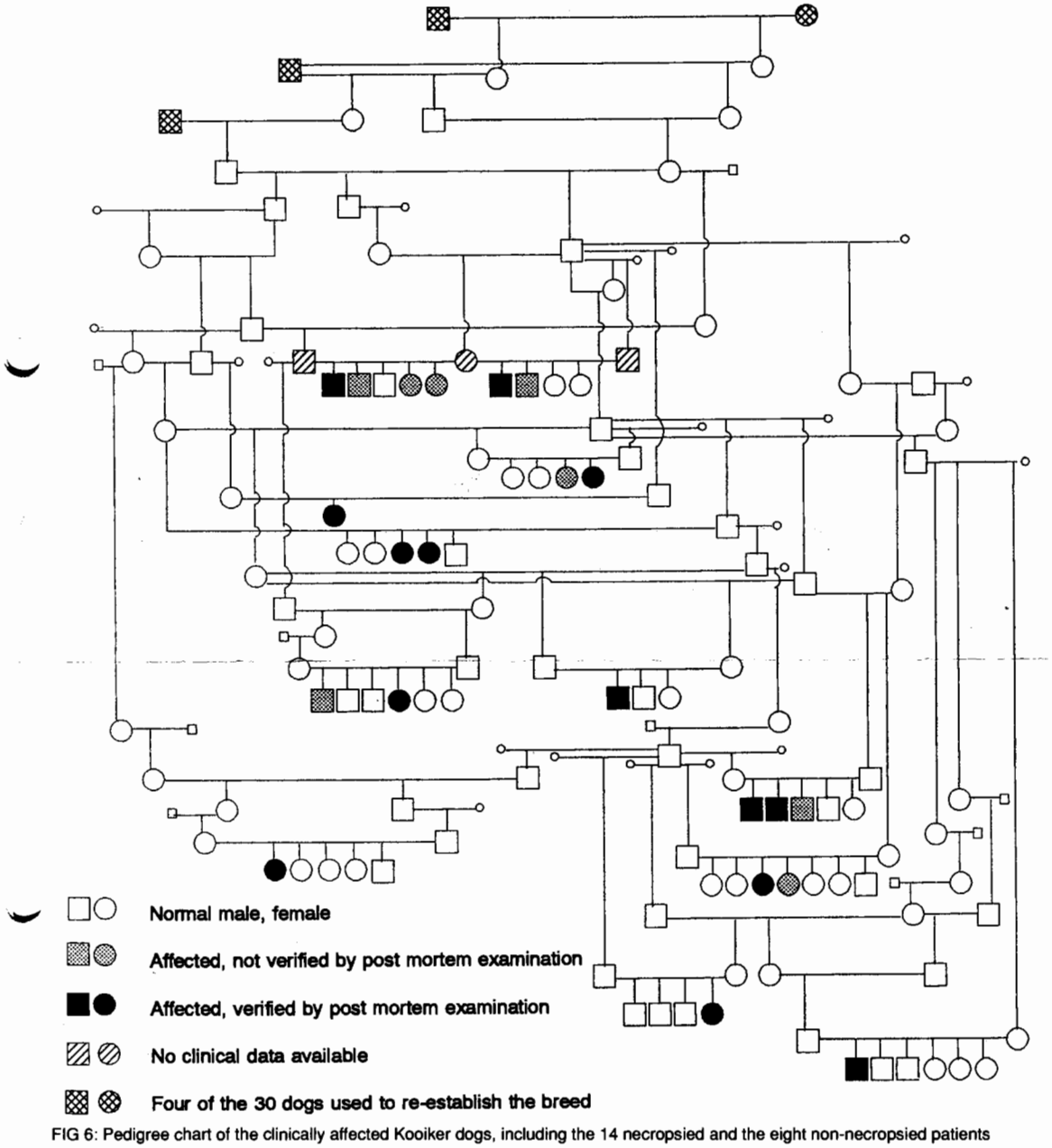

FIG 6: Pedigree chart of the clinically affected Kooiker dogs, including the 14 necropsied and the eight non-necropsied patients

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 II, 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 olivaris 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 0·1272 to 0·3592, with a median of 0·2296.

These levels of inbreeding differ significantly (P=0·001). The general population were descended from 30 dogs, while all the affected dogs were descended from one pair and only four in all of the original 30 dogs (Fig 6).

No clinical data were available for three of the parents of these 22 patients and therefore two litters had to be excluded (Fig 6). The remaining litters comprised 10 affected females and six affected males but this gender difference was not significant (P>0·05). Using the hypothesis that both parents were carriers, the expected segregation 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 'Kooikerparalysis' were mentioned in a clinical lecture by Verwer (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 at the border of the necrotic lesions in the white matter in the 14 necropsied dogs suggests primary demyelination. It is reasonable to relate the apparent neurological deficits to the necrotic and Wallerian lesions in the ascending as well as descending fibre tracts (Rasminsky 1980).

The clinical and pathological findings have much in common with those of hereditary myelopathy in Afghan hounds (Cummings and de Lahunta 1978) and leucoencephalomyelopathy in rottweilers (Gamble and Chrisman 1984, Wouda and Van Nes 1986).

Afghan myelopathy causes ataxia and rapidly progressive paralysis. The lesions, mainly located in the low cervical and mid-thoracic spinal cord, consist of myelinolysis and malacia rather than dysmyelinogenesis, and have been compared with myelinopathies of toxic/metabolic origin (Cummings and de Lahunta 1978).

In rottweiler leucoencephalomyelopathy, older animals (1·5 to 3·5 years) develop a slowly progressive ataxia and paresis. Symmetrical lesions have been found in the spinal cord, brainstem and cerebellum. Both demyelination and remyelination have been observed (Wouda and Van Nes 1986). Gamble and Chrisman (1984) suggested a vitamin B_{12} deficiency. A myelopathy associated with vitamin B_{12} deficiency is known in humans to begin in the thoracic spinal cord and to affect all funiculi (Adams and Sidman 1968). In English foxhounds and harriers, diffuse degeneration of white matter was described as being associated with vitamin B_{12} deficiency caused by feeding ruminant stomachs (Sheahan et al 1991). In the Kooiker dogs the lesions were more localised.

The clinical and pathological findings in these 22 purebred Kooiker dogs suggest a leucodystrophic type of disease. The mode of inheritance one often finds in leucodystrophy is simple Mendelian inheritance (Crome and Stern 1976). There are strong indications of heritability including 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 inheritance. 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 (Willis 1989). The observed symmetry, primary demyelination and the apparent heritability in Kooiker dogs as well as in Afghan hounds and rottweilers are strong reasons for classifying all of these neurological disorders as leucodystrophic diseases.

Acknowledgements

The authors thank Professor G. J. W. van der Mey for his comments on the pedigree data, Dr J. van den Broek for his assistance in the statistical analysis and Dr M. G. T. H. van Schaik for her help in collecting the pedigree data. Mr G. van Asperen and Mr R. Nooteboom of the Association of the Dutch Kooiker Dog kindly provided the necessary pedigree data.

References

ADAMS, R. D. & SIDMAN, R. L. (1968) Introduction to Neuropathology, New York, McGraw-Hill

ARMITAGE, P. & BERRY, G. (1988) Statistical Methods in Medical Research. 2nd edn. Oxford, Blackwell Scientific Publications

AVERILL, D. R. & BRONSON, R. T. (1977) Inherited necrotising myelopathy of Afghan hounds. *Journal of Neuropathology and Experimental Neurology* **36**, 734-747

BICHSEL, P. M., VANDEVELDE, M., LANG, J. & KULL-HACHLER, S. (1983) Degenerative myelopathy in a family of Siberian Husky dogs. *Journal of the American Veterinary Medical Association* **183**, 998-1000

BRAUND, K. G. & VANDEVELDE, M. (1978) German Shepherd dog myelopathy – A morphologic and morphometric study. *American Journal of Veterinary Research* **39**, 1309-1315

CROME, L. & STERN, J. (1976) Inborn lysosomal enzyme deficiencies. In Greenfield's Neuropathology. Eds W. Blackwood and J. Corsellis. 3rd edn. London, Edward Arnold. pp541-557

CUMMINGS, J. F. & LAHUNTA, A. DE (1978) Hereditary myelopathy of Afghan hounds: a myelinolytic disease. *Acta Neuropathologica* (Berlin) **42**, 173-181

GAMBLE, D. A. & CHRISMAN, C. L. (1984) A leucoencephalomyelopathy of Rottweiler dogs. *Veterinary Pathology* **21**, 274-280

LAHUNTA, A. DE (1983) Veterinary Neuroanatomy and Clinical Neurology. 2nd edn. Philadelphia, W. B. Saunders. pp200-204

LONGHOFER, S. L., DUNCAN, I. D. & MESSING, A. (1990) A degenerative myelopathy in young German shepherd dogs. *Journal of Small Animal Practice* **31**, 199-203

PATTERSON, D. F., AGUIRRE, G. A., FYFE, J. C., GIGER, U., GREEN, P. L., HASKINS, M. E., JEZYK, P. F. & MEYERS-WALLEN, V. N. (1989) Is this a genetic disease? *Journal of Small Animal Practice* **30**, 127-139

RASMINSKY, M. (1980) Physiological consequences of demyelinisation In Experimental and Clinical Neurotoxicology. Eds P. S. Spencer and H. H. Schaumburg. Baltimore, Williams & Wilkins. pp257-271

SHEAHAN, B. J., CAFFREY, J. F., GUNN, H. M. & KEATING, J. N. (1991) Structural and biochemical changes in a spinal myelinopathy in twelve English foxhounds and two harriers. *Veterinary Pathology* **28**, 117-124

VANDEVELDE, M. (1980) Degenerative diseases of the spinal cord in veterinary neurology. *Veterinary Clinics of North America: Small Animal Practice* **10**, 147-154

VERWER, M. A. J. (1968) Paraparesis posterior in honden. *Tijdschrift voor Diergeneeskunde* **93**, 828-837

WILLIS, M. B. (1989) Genetics of the Dog. London, H. F. & G. Whitherby. pp320-332

WHEELER, S. J. (1989) Diagnosis of spinal diseases in dogs. *Journal of Small Animal Practice* **30**, 81-91

WOUDA, W. & VAN NES, J. J. (1986) Progressive ataxia due to central demyelination in Rottweiler dogs. *Veterinary Quarterly* **8**, 289-297

WRIGHT, S. (1922) Coefficient of inbreeding and relationship. *American Nature* **56**, 330-339

Received April 28, 1992
Accepted July 27, 1992