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Ceroid-lipofuscinosis in Border Collie dogs

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Summary. Five Border Collie dogs with ceroid-lipofuscinosis developed progressive neurological disease between 18 and 22 months of age. These dogs had behavioural abnormalities, gait and visual deficits and became progressively demented. All dogs examined had common ancestors. Light microscopic examination of tissues demonstrated extensive accumulation of granular, sudan black-staining autofluorescent material in the cytoplasm of neurones, retinal ganglion cells and some visceral cells. At ultrastructural examination inclusions of variable morphology were observed.

Key words: Canine ceroid-lipofuscinosis – Animal model

Ceroid-lipofuscinosis is an inherited disorder, which occurs in man and animals, and is characterized by widespread lipopigment accumulation in neurovisceral tissues and clinical signs of neurological disease. The metabolic errors underlying the ceroid-lipofuscinoses have not been found, despite extensive study.

Juvenile canine ceroid-lipofuscinosis has been described in English Setters [5], Chihuahuas [8], Salukis [1], Dalmatians [3] and a Blue Heeler dog [2]. The affected dogs developed clinical signs of neurological disease before 2 years of age, which progressed rapidly until the animals died at 2–3 years of age. The principal findings were blindness, behavioural change, and gait deficits [6]. In this report we describe five Border Collie dogs with clinical signs and histopathological lesions similar to those reported in English Setters and other dogs with ceroid-lipofuscinosis.

Materials and methods

Five affected dogs were examined clinically, necropsied and tissues were collected and processed for light and electron microscopy. The pedigree details of the five animals are presented in Fig. 1.

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Results

The five dogs comprised three males and two females. They were purebred Border Collie dogs aged between 18 and 24 months at presentation. All dogs had developed progressive behavioural changes over several months. When examined they were hyperactive, unresponsive to stimuli and three animals could not be fully examined due to their demented behaviour. Mild ataxia and delayed postural reactions were present and one animal had an intermittent head tilt. They appeared to be blind, had bilateral loss of menace responses and slow pupillary light reflexes. No abnormalities were found on fundoscopy, routine haematology and biochemical tests or on cerebrospinal fluid examination.

Affected dogs of both sexes were fertile. The parents of the probands were not affected (Fig. 1). The pedigree findings are consistent with an autosomal recessive mode of inheritance, however no breeding trials were performed.

At necropsy the cerebellum appeared smaller than normal in two dogs, but this observation was not confirmed quantitatively. Microscopic examination revealed eosinophilic, sudanophilic storage granules in the neuronal perikarya and the glial cytoplasm throughout the brain and spinal cord (Fig. 2). In the cerebellum severe loss of Purkinje cells and reduction in the numbers of granule cells were observed. The remaining Purkinje cells contained eosinophilic, autofluorescent granules. Macrophages with pigmented granules were found in the molecular cell layer and adjacent to areas of Purkinje cell loss. The cerebellar roof nuclei were extensively granulated and eosinophilic axonal swellings were present. A mild gliosis was observed throughout the central nervous system. Some cerebrocortical neurones were lost and scattered

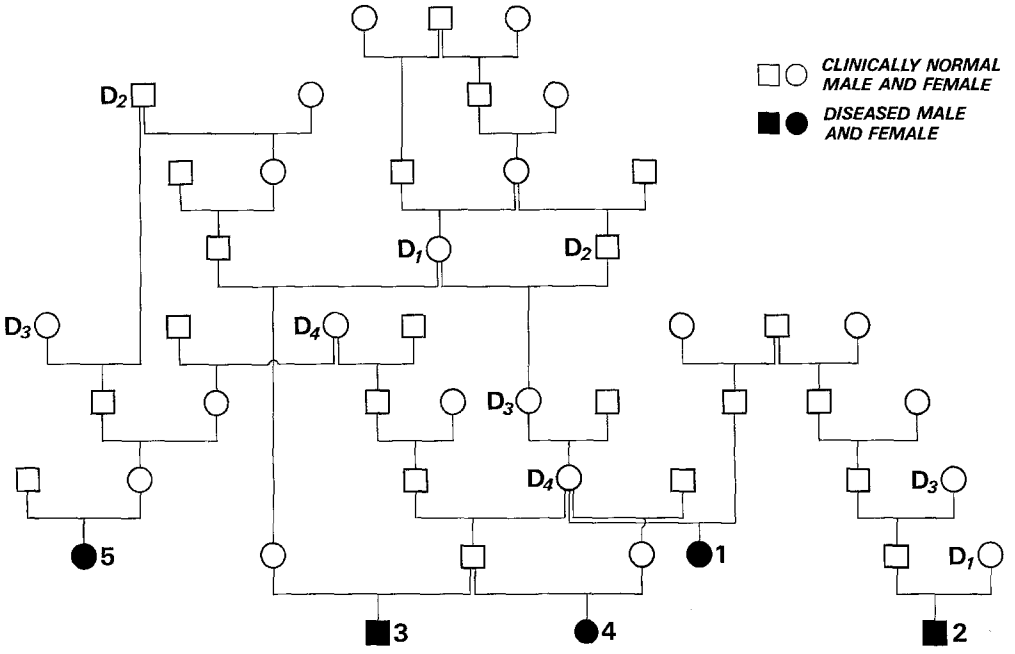

Fig. 1. Pedigrees of the five affected dogs, highlighting the common ancestors (numbered $D_1 - D_4$). The affected animals are indicated by the numbers 1 – 5

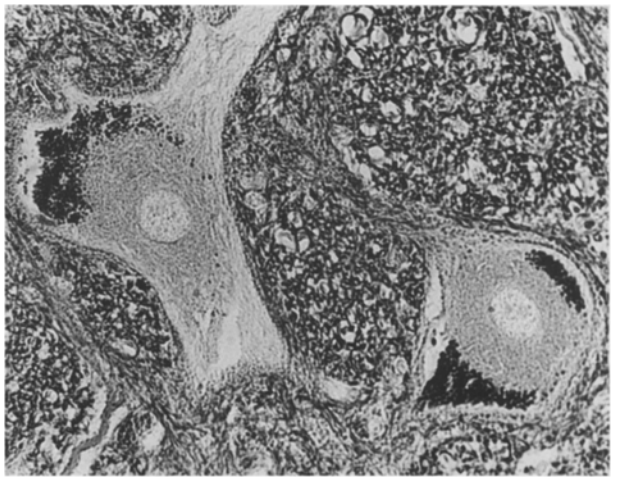

Fig. 2. Midbrain. Two neurones with peripheral clusters of sudanophilic storage material. Sudan Black, ×206

macrophages with granular cytoplasm were observed in the parenchyma, perivascular spaces and the leptomeninges. The degree of granule accumulation was not uniform; some neurones and many glial cells were unaffected in the cerebral cortex, while almost all neurones in the hippocampus, thalamus and pons contained storage material. The spinal cord ventral and lateral horn cells were pigmented. The ganglion cells of the retina contained granular material. Green-yellow autofluorescence was observed in cells of the cerebrum, cerebellum and spinal cord.

Peribronchial phagocytes, hepatic Kupffer cells and macrophages in the spleen contained storage granules. The renal tubular epithelium, thyroid epithelial cells, enteric ganglia and submucosal plexus cells contained small, refractile, sudanophilic granules.

Most neurones and some glial cells in the central nervous system contained inclusion bodies at ultrastructural examination. The areas of lipopigment accumulation varied in size from small discrete bodies (Fig. 3) to large poorly defined areas in the cytoplasm (Fig. 4). The inclusion outlines were highly irregular and although single limiting membranes were present around some bodies, others appeared to be free in the cytoplasm. Frequently several different patterns of storage material were present within one cell and even within the same cytosome. A variety of granular and membranous inclusions were found resembling the curvilinear (Fig. 4), fingerprint (Fig. 3), crystalloid and zebra bodies described in other ceroidoses.

The cytosomes seen in the retina were more specific to particular cell types. The ganglion cells contained irregular clusters of loosely packed, curved material. The bipolar cells had inclusions composed of tightly packed parallel membranes (Fig. 5). These forms were interspersed with more amorphous, ill-defined material, which was often free in the cytoplasm. The photoreceptor cells contained rounded, faintly osmiophilic, curved profiles. No storage material was found ultrastructurally in the sciatic nerve. The epididymal

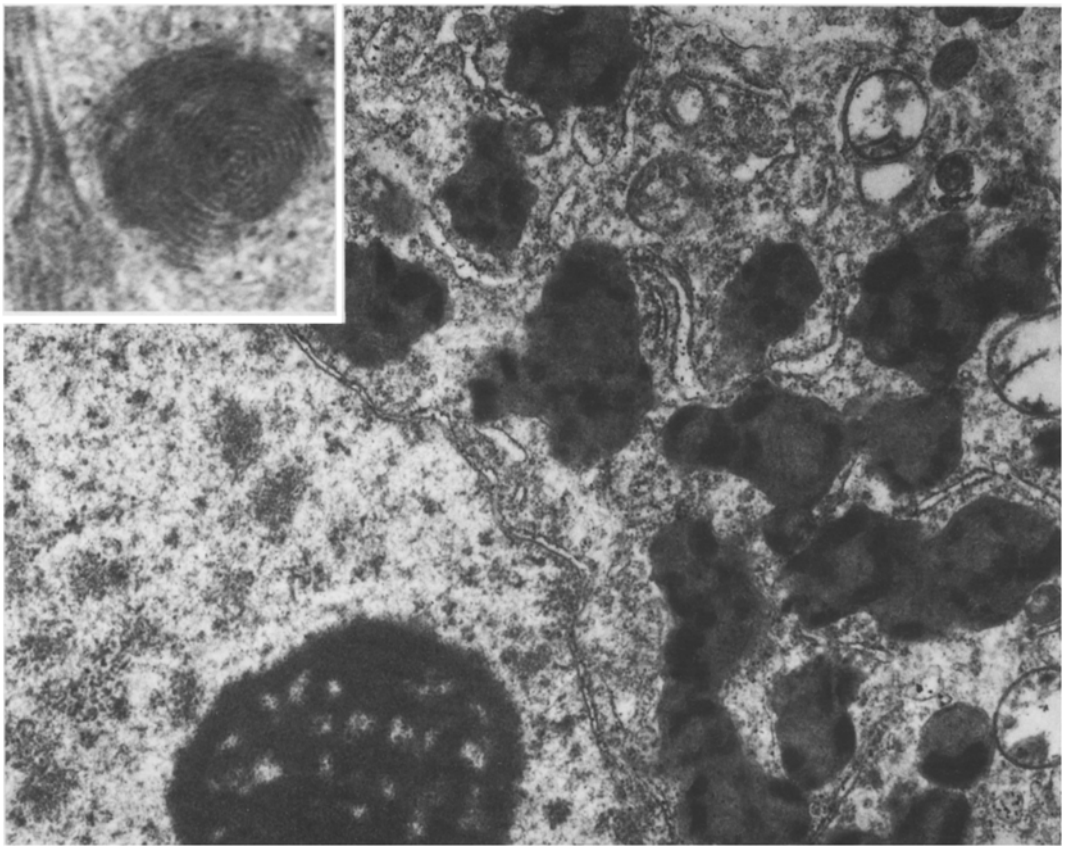

Fig. 3. Medulla. Curvilinear and crystalloid forms of storage material of variable density are present in the neurones. The enlargement shows the fingerprint patterns found in the dense inclusions. ×17,786; *insert* ×62,095

epithelium contained inclusions with a homogenous, lipoid and curvilinear appearance (Fig. 6).

Discussion

Ceroid-lipofuscinosis in the Border Collie is highly analogous to the disease in English Setter dogs. Although lipopigment storage lesions were found throughout the body, granule accumulation was most severe in the central nervous system and the clinical signs were principally of neurological disease in affected Border Collies. Blindness and dementia progressed rapidly after 18 months of age. The clinical and pathological findings also resembled those of canine ceroid-lipofuscinosis in Chihuahuas, a Blue Heeler, Dalmatians and Salukis, although gait deficits were less severe in the Border Collie dogs.

The pathological lesions were most severe in central nervous system and correlated with the clinical signs of motor, mental and visual deterioration. Gliosis and neurone loss, particularly in the Purkinje cell layer of the cerebellum was severe. Peripheral neurones in the intestine were also affected, however no evidence of storage lesions in the peripheral nerve axons or Schwann cells was found. The tinctorial properties of the storage material were identical to those described in other cases of juvenile canine ceroid-lipofuscinosis.

In contrast to childhood ceroid-lipofuscinosis, which is characterized by a progressive retinopathy [10], only mild retinal lesions occur in canine ceroid-lipofuscinosis [4]. The visual impairment in the Border Collies most closely resembled that recorded in English Setters with ceroid-lipofuscinosis. The dogs had normal retinal structure with fundoscopic and light microscopic examination, but extensive ultrastructural lesions. In affected English Setters the early loss of vision is due to progressive, severe cerebrocortical neuronal damage. This occurs in the absence of light microscopic evidence of retinal damage [7]. The retinal lesions in both canine models contrast with the severe, early retinal deterioration and electroretinogram changes seen in juvenile Batten's disease.

The biochemical basis of the ceroid-lipofuscinoses remain unresolved despite intensive study. Wolfe et

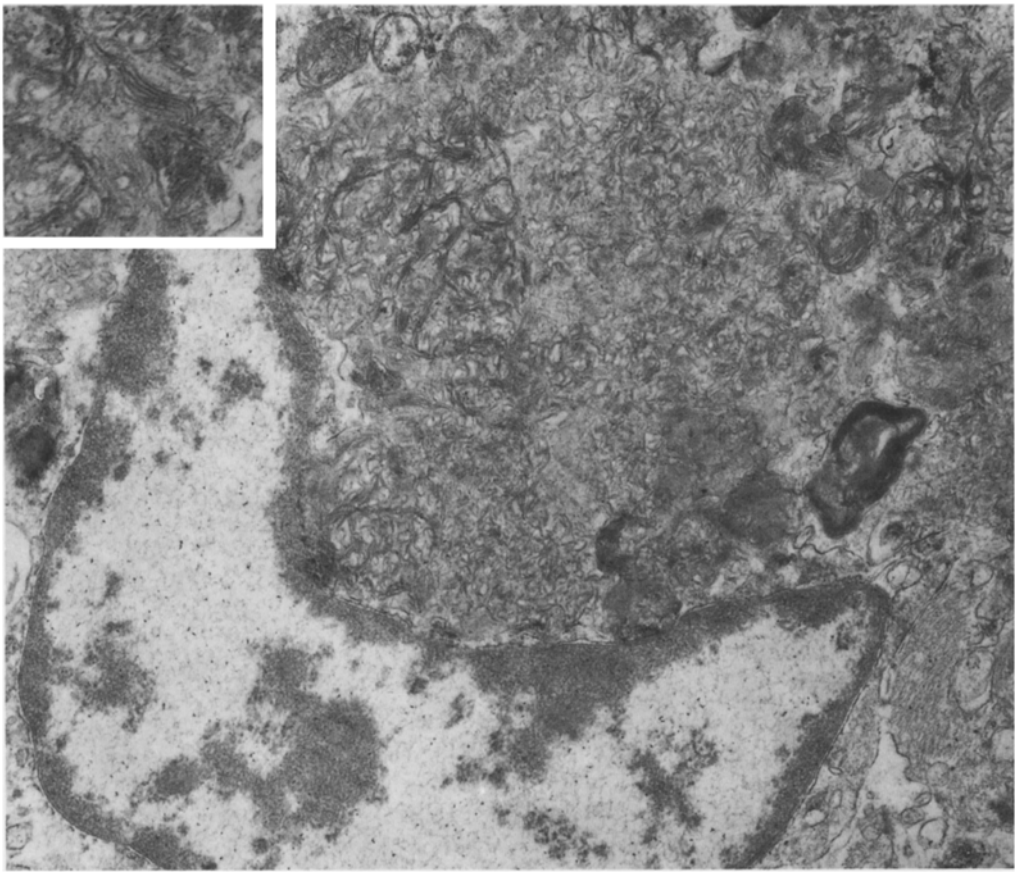

Fig. 4. Cerebellum. Curvilinear, ill-defined inclusions (*insert*) fill the cytoplasm. ×17,786; *insert* ×35,890

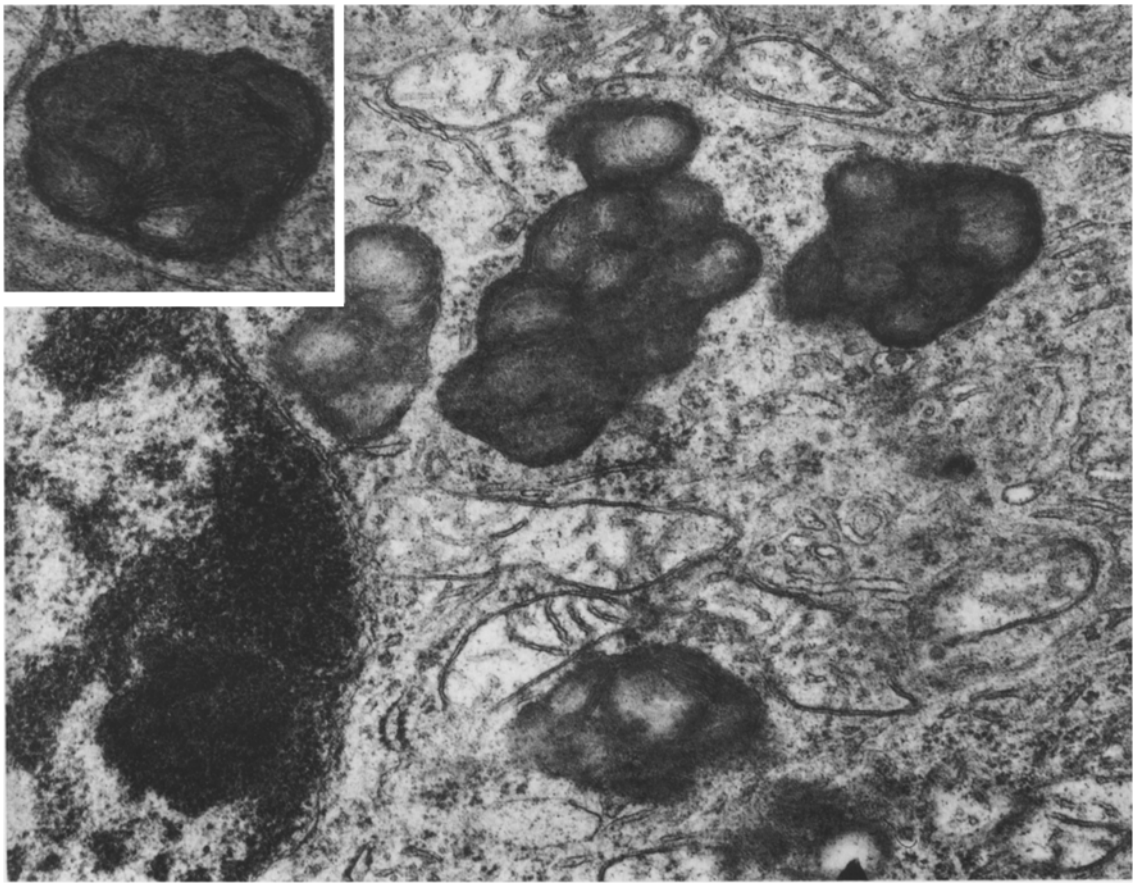

Fig. 5. Retina. Bipolar cells with dense, irregular inclusions. The inclusions (*insert*) have curved stacks of parallel membranes with an amorphous central area. ×29,590; *insert* ×34,980

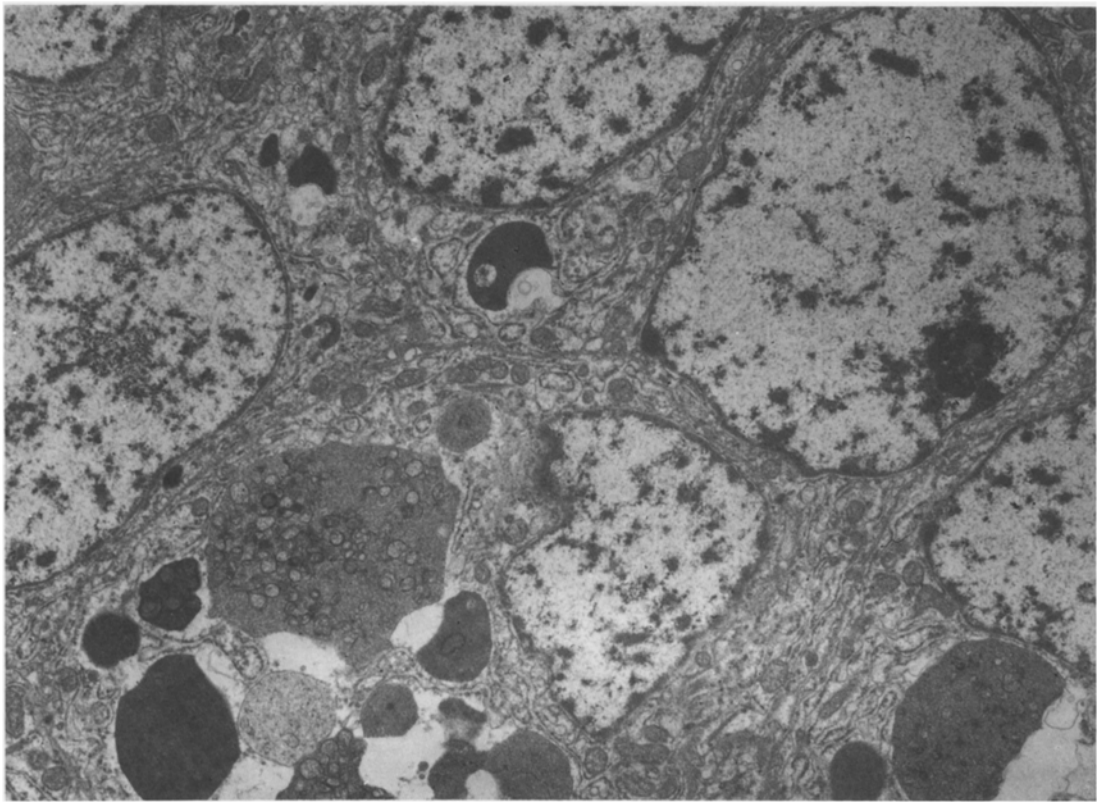

Fig. 6. Epididymal epithelial cell. Cytosomes with dense, lipoid, homogenous material and curved, membranous profiles are present. ×8,182

al. [9] have suggested a defect in thiol endoprotease activity, which might cause accumulation of lysosomal membranes. This animal model has considerable potential for preclinical studies of the pathogenesis and treatment of Batten's disease.

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