CEREBELLAR DISEASE IN THE DOG AND CAT:

A LITERATURE REVIEW AND CLINICAL CASE STUDY (1996-1998)

by

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SUMMARY

The aim of this thesis is to detail the history, clinical findings, ancillary investigations and, in some cases, pathological findings in 25 cases of cerebellar disease in dogs and cats which were presented to Glasgow University Veterinary School and Hospital during the period October 1996 to June 1998. Clinical findings were usually characteristic, although the signs could range from mild tremor and ataxia to severe generalised ataxia causing frequent falling over and difficulty in locomotion. Diffuse cerebellar diseases were more common than focal in this study. Both dogs and cats are susceptible to cerebellar diseases, however, the aetiologies vary between these two species. In the dog, inflammatory disease of unknown aetiology (or steroid- responsive tremor syndrome) was the most common cause of cerebellar disease, affecting ten out of fourteen cases. In contrast, cerebellar hypoplasia possibly caused by panleukopaenia virus was the most common cause of cerebellar signs in the cats, affecting four out of eleven cases, while only one dog was diagnosed with a developmental abnormaly. Inflammatory cerebellar disease in the cats was caused most commonly by feline infectious peritonitis virus, which was diagnosed in two cats. Feline spongiform encephalopathy occurred in two cats. Degenerative cerebellar disorder was diagnosed in three cases, with a definite diagnosis of abiotrophy in two cases and lysosomal storage disease in a cat. Trauma or angiopathy was suspected in two cases. Cerebellar neoplasia was relatively rare, and was diagnosed only in one dog.

A thorough physical and neurological examination was important in localising the lesion and determining whether a multisystemic disease was present. However, in most cases, a definite diagnosis could not be achieved on the basis of history and clinical findings. CSF analysis was found to be useful in some cases, especially in ruling in an inflammatory cause. The definitive diagnosis was made by histopathological examination in six cases. The pathological findings are discussed in relation to the literature.

DECLARATION

The work in this thesis was carried out by myself,

except where appropriately acknowledged,

and has not been submitted previously

for the award of a degree at any other university.

Diane Dah-An Lu

To my family and Mei-Yee

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ACKNOWLEDGEMENTS

"Without me, ye can do nothing." John 15:5

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INTRODUCTION

The cerebellum is a very well-defined structure, identified on gross examination of the dorsal aspect of the caudal brain stem, located in the caudal fossa of the calvarium. The cerebellum receives information concerning the activity being initiated from motor centres, proprioceptive information from the limbs and trunk regarding their position in space, and information from the ocular and vestibular systems regarding the posture of the head. The cerebellum functions by co-ordinating muscular activity. Any disease process interfering with the information entering or leaving the cerebellum, or causing primary dysfunction of the cerebellum, will potentially result in cerebellar dysfunction. In this thesis, the term cerebellar disease is used to describe conditions affecting predominately the cerebellum, excluding diseases affecting the related tracts. Cerebellar dysfunction produces clinical features, characteristically including generalised ataxia, dysmetria (hypermetria), wide-based stance, falling over, intention tremor, generalised tremor, and occasionally absence of menace response. However, not all the signs mentioned above are demonstrated in every case.

The cerebellum is susceptible to a wide range of disease processes, which may be confined to this region, or form part of a multisystem disease. The cerebellum is particularly susceptible to degenerative processes such as lysosomal storage diseases and abiotrophies. Congenital diseases such as malformations and dysmyelinosis, occur sporadically in dogs and cats. Very rare intermediary metabolic disorders may produce cerebellar signs. Medulloblastoma is a specific cerebellar tumour, and other primary or secondary intracranial neoplasia may involve the cerebellum. Cerebellar signs may occur during the progressive course of thiamine deficiency. Infectious and inflammatory diseases are usually multifocal, although some inflammatory diseases, especially those of unknown aetiology, may present with predominately cerebellar signs. Several toxins such as lead, metaldehyde, hexachlorophene and some other plant or fungi toxins may produce signs suggestive of cerebellar dysfunction. Head injury may cause cerebellar damage. Vascular disease such as infarction and haemorrhage can occur rarely in the cerebellum in dogs and cats.

As in human medicine, the disorders of the cerebellum can be localised only in the broadest and most general terms; specific point-to-point representations of body parts or discrete physiologic functions in the cerebellum apply only to the experimental animal under certain conditions (Gilman *et al.* 1981). A basic knowledge of the embryological development, anatomy and physiology of the cerebellum together with the principles of localisation of cerebellar disorders is therefore vital to the understanding of cerebellar disease.

SECTION I.

LITERATURE REVIEW

1.1 EMBRYOLOGICAL DEVELOPMENT OF THE CEREBELLUM

The central nervous system (CNS) first appears as a dorsal thickening of the ectoderm, the neural plate, which occurs at around the 17th gestation day in the dog (63-day gestation length) and the 13th gestation day in the cat (62 day gestation length) (Noden & de Lahunta 1985). Its lateral edges become elevated to form the neural folds which eventually meet in the midline and fuse to form the neural tube. The cephalic end of the neural tube forms three vesicular enlargements: prosencephalon or forebrain, mesencephalon or midbrain, and rhombencephalon or hindbrain (Noden & de Lahunta 1985, Beitz & Fletcher 1993). The rhombencephalon further develops into two parts, the metencephalon which later forms the pons and cerebellum, and the myelencephalon. The wall of the neural tube develops into 3 layers, from innermost to outermost, they are the germinal or ventricular zone, which is the region of active cell division; the mantle or intermediate zone which consists of proliferating neurepithelial cells, immature neurones and presumptive glial cells; and the marginal layer, which contains the axonal processes of developing neurones (Noden & de Lahunta 1985, Latshaw 1987). The neural tube forming the rhombencephalon and future spinal cord subdivides in a dorsoventral manner into the alar (sensory) and basal (motor) plates respectively.

The cerebellum develops as dorsolateral outpouchings from the alar plate region of the metencephalon (Figure 1A), termed the rhombic lips. These extend the alar plate tissue dorsally and medially to ultimately join each other by an isthmus. At the end of development, the rhombic lips form the lateral hemispheres and the isthmus forms the vermis (including the floccular-nodular area) (Latshaw 1987). Embryonically the first cerebellar fissure to appear is the caudolateral fissure (or the uvulonodular fissure), which separates the flocculonodular lobe caudally from the body of the cerebellum rostrally. Further differentiation results in the flocculonodular lobe remaining small and the body of the cerebellum enlarging to form most of the cerebellar mass. The next fissure to develop is the primary fissure, which separates the rostral and caudal lobes of the cerebellar body (Jenkins 1978).

Initially, the cells in the germinal layer adjacent to the fourth ventricle (de Lahunta 1983) migrate radially towards the surface to form a mantle layer (Latshaw 1987). The differentiating mantle layer cells migrate into the substance of the rhombic lip. These immature neurones cease division but continue to grow and mature, giving rise to the Purkinje cell layer, Golgi cells and the neurones of the deep cerebellar nuclei. Another migration phase occurs in the germinal layer at the lateral region of the rhombic lips (Latshaw 1987). These germinal cells

migrate to the rhombic lip surface and continue mitosis, producing a zone of 10-12 layers of germinal cells, termed the external germinal layer, on the surface of the developing cerebellum (Figure 1B). Differentiation occurs along the inner aspect of these cells, and those that cease mitosis migrate to the level of, or deep to the Purkinje cells and form the granule neurone layer (de Lahunta 1983, Latshaw 1987). Those cells that migrate to a more superficial location form the stellate, basket and glial cells of the molecular layer. As the cerebellum grows, the cortex forms folds called folia. The granule layer is thickest over the centre of each folium and thinner around the depths of the sulci (Noden & de Lahunta 1987). When the cellular migration has finished, the external germinal layer regresses and only the leptomeninges remain on the surface of the molecular layer (de Lahunta 1983).

The pattern of cellular differentiation appears to be reproducible from species to species and differs primarily as it relates to gestational age and functional requirements at birth. It is known that the degree of cerebellar development at birth correlates with the amount of motor function and co-ordination seen in the new-born animal (cited in de Lahunta 1983). A direct correlation has been shown between the development of the cerebellar cortex and mobility of the kitten (de Lahunta 1983). In general, the animals that can walk at birth (e.g. foal and calf) have a more completely developed cerebellum than the kitten or the puppies which cannot walk at birth.

In carnivores, much of the differentiation of the cerebellar cortex occurs postnatally (Latshaw 1987). Purkinje neurones are formed and begin differentiation early in the development of the embryo (de Lahunta 1983). The Purkinje cells gradually increase in size but do not attain their full mature structure until around the 10^{th} postnatal week (Phemister & Young 1968). Similarly, the granule neurone layer is present at birth but is poorly populated and continues to develop for up to ten weeks postnatally in dogs (Phemister & Young 1968).

The external germinal layer is active late in gestation and even after birth in some species. In the puppy the width of the external germinal layer remains relatively constant in the first two postnatal weeks and starts to decrease in size after the second postnatal week (Phemister & Young 1968). Whereas in the kitten, there is an increase in thickness during the first postnatal week followed by a steady decline beginning at two weeks (Smith & Downs 1978). External germinal layers cells will persist for up to 60-84 days in the kitten, 72 days in the puppy (Phemister & Young 1968). However, Moustafa (1996) reported that the external granular layer reached its maximum thickness during gestation, then it decreased with age until it disappeared in most areas of cerebellar cortex in the postnatal 45 days-old dog.

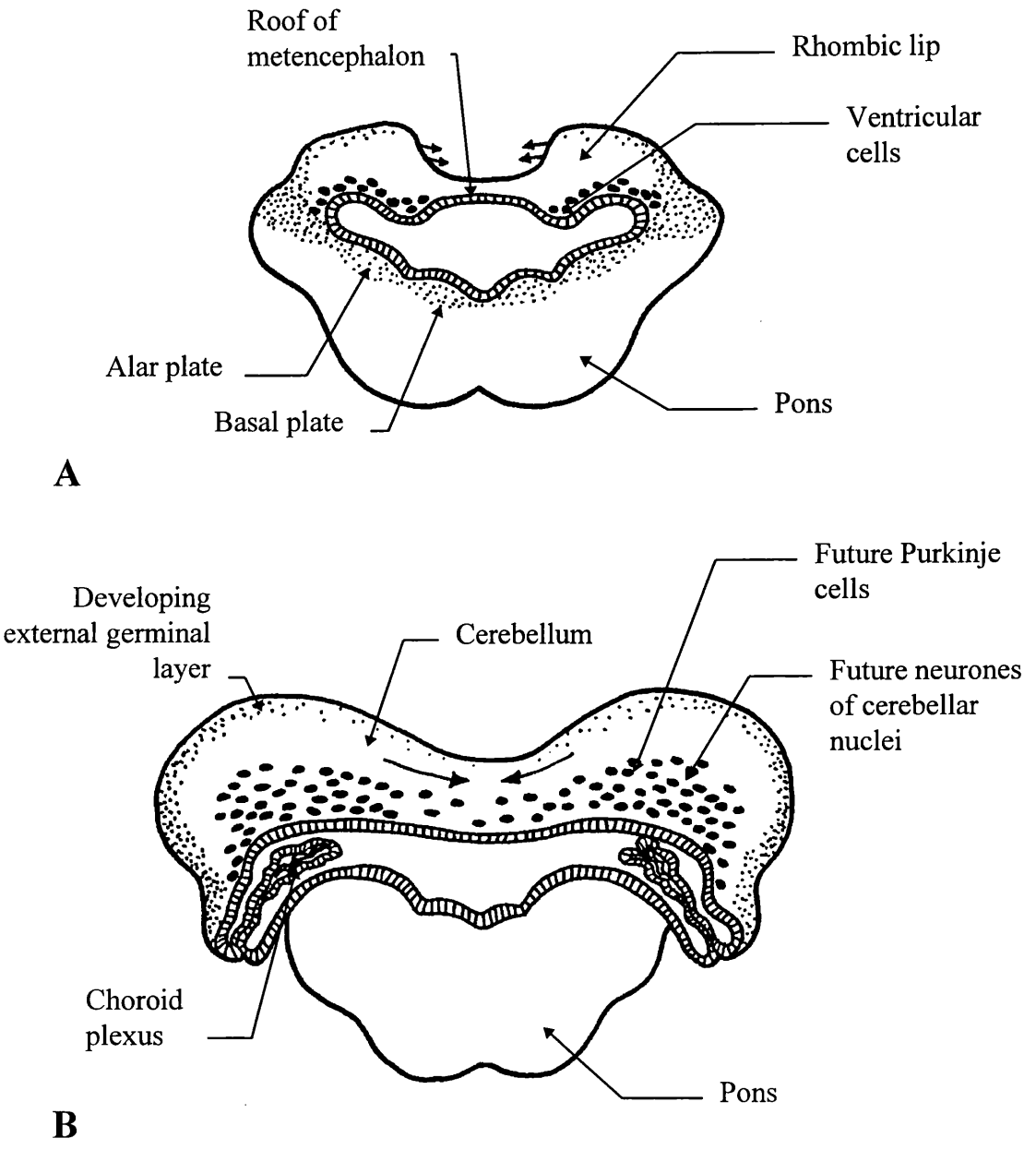

Figure 1. Development of the cerebellum.

A. Growth of rhombic lips with medial fusion to form isthmus.

B. Migration of germinal cells forming Purkinje neurones, deep cerebellar nuclei, Golgi cells; and development of external germinal layer.

Arrows indicate the direction of cell migration.

(Modified from Noden & De Lahunta, 1985)

1.2 NEUROANATOMY OF THE CEREBELLUM

1.2.1 Gross anatomy

The cerebellum is the caudal superstructure of the brain (Jenkins 1978). It lies caudal to the occipital lobes of the cerebral hemispheres, from which it is separated *in vivo* by the osseous tentorium and the tentorium cerebelli within the transverse cerebral fissure (Jenkins 1978, King 1987). It lies dorsal to the pons and medulla oblongata, and is separated from the fourth ventricle by the rostral and caudal medullary velum which is the thin, tent-like dorsal roof to the fourth ventricle (King 1987). Within the calvaria, the cerebellum fills much of the caudal fossa. The choroid plexuses of the fourth ventricle project through the lateral apertures into the subarachnoid space and lie in the cerebellopontine angle.

The gross configuration of the cerebellum (Latin: *little brain*) is analogous to cauliflower with a hilus, and is attached to the brain stem by three pairs of cerebellar peduncles (Jenkins 1978). Median sectioning of the cerebellum reveals several similarities to the cerebrum: the cerebellum has a peripheral cortex (*cortex cerebelli*) composed of grey matter and a central medulla composed mainly of white matter. The cerebellar cortex consists of long slender convolutions, named folia (L. *folium*, a leaf; *folia*, leaves of a book) (*folia cerebelli*) which are separated by grooves called the cerebellar sulci (*sulci cerebelli*), thereby corresponding to the gyri and sulci of the cerebrum. Moreover, there are three pairs of deep cerebellar nuclei embedded in the cerebellar white matter, from medial to lateral, they are fastigial nucleus (*nucleus fastigii*), interposital nucleus (*nucleus interpositus cerebelli*) and dentate nucleus (*nucleus lateralis cerebelli*), which, by being deeply located grey matter, resemble the basal nuclei in the cerebral white matter (Jenkins 1978, Beitz & Fletcher 1993).

Grossly, from dorsolateral view (Figure 2), the cerebellum consists of three principal divisions: a central median band, the vermis (L. worm), named for its resemblance to a worm, and on each side of the vermis are the lateral lobes, termed cerebellar hemispheres (*hemispherium cerebelli*) (Jenkins 1978, Beitz & Fletcher 1993). Externally, the cerebellum is subdivided into three lobes by two transverse fissures. The uvulonodular (or caudolateral) fissure (*fissura uvulonodularis*) separates the cerebellum into a main, larger mass, the cerebellar body (*corpus cerebelli*) and a small, ventral flocculonodular lobe (*lobus flocculonodularis*). The larger body can be further divided into a rostral lobe (*lobus rostralis*) and a caudal lobe (*lobus caudalis*) by the dorsally located primary fissure (*fissura prima*) (de Lahunta 1983, Beitz & Fletcher 1993). The hemispheres can be further subdivided into lobules. The caudal lobe contains the

anisformis, paramedianus, dorsal and ventral paraflocculus, lobulus simplex; the rostral lobe consists of the quadrangular, vinculum lingulae and ala lobulus centralis. The flocculus forms the lateral portion of the flocculonodular lobe (Beitz & Fletcher 1993).

In the sagittal view of cerebellum, the general appearance of the folia, sulci, fissures and the projections of the white matter extending into the substance of the folia resembles the appearance of an evergreen shrub or tree, thus it is often referred to as the arbor vitae (L. tree of life) (Jenkins 1978, King 1987). On sagittal section, nine lobules can be demonstrated within the cerebellar vermis, which are marked by fissures less distinct than the uvulonodular fissure. Using the classic nomenclature that is applicable to both human and other mammals (cited in Jenkins 1978), the lobules in a rostrocaudal sequence are lingula, central lobule, culmen, declive, folium, tuber, pyramis, uvula, and nodulus (Figure 3). The nodulus is the most rostral part of the caudal vermis that is adjacent to the fourth ventricle (de Lahunta 1983). Other methods of nomenclature are also used. One very commonly used is by Larsell (1953), in which he designates 10 primary lobules in mammals, as indicated by Roman numerals (Table 1).

The cerebellum is attached bilaterally to the brain stem by nerve fibres organised into three pairs of cerebellar peduncles. Although they appear in a medio-lateral orientation in cross section, they are named in a rostral-caudal relationship based on their connections with the brain stem (de Lahunta 1983). The rostral cerebellar peduncle (*brachium conjunctivum*) connects the cerebellum with the mesencephalon, and contains mainly efferent processes from the cerebellum. The middle cerebellar peduncle (*brachium pontis*) connects the transverse fibres of the pons with the cerebellum, and is entirely afferent to the cerebellum. The caudal cerebellar peduncle connects the spinal cord and medulla with the cerebellum, and contains both afferent and efferent processes. The caudal peduncle is composed of two components: a restiform body (*corpus restiforme*) and a juxtarestiform body (*corpus juxtarestiforme*) (Beitz & Fletcher 1993). The latter refers to a small separate bundle on the medial aspect of the caudal peduncle, which carries the afferent and efferent vestibulocerebellar fibres (King 1987).

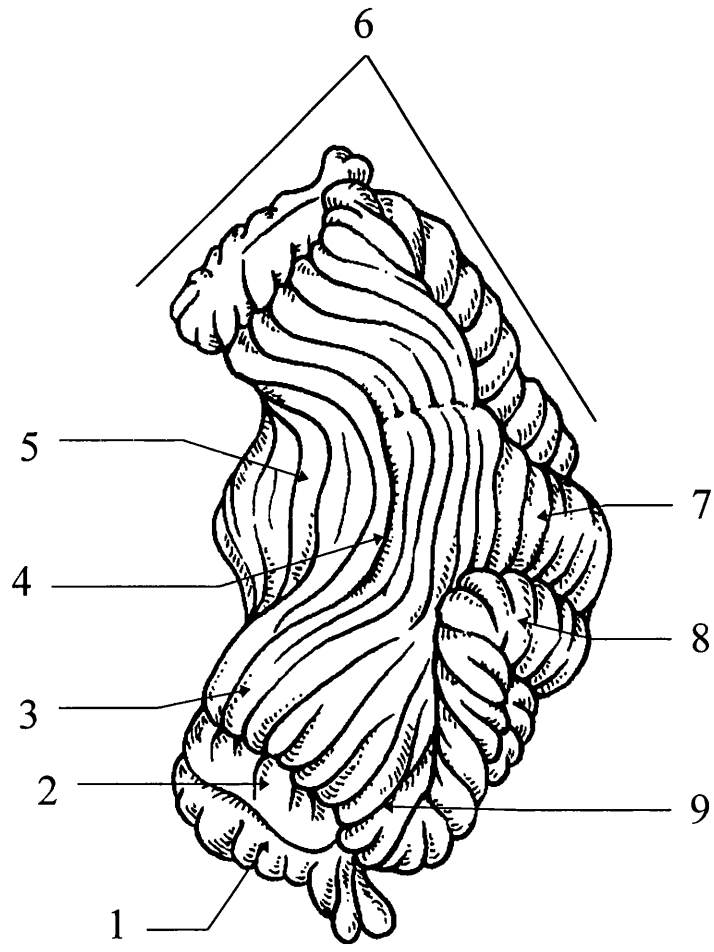

Figure 2. Dorsolateral view of the cerebellum.

1. Ventral paraflocculus
2. Dorsal paraflocculus
3. Lobulus simplex
4. Primary fissure
5. Vermis portion of rostral lobe
6. Right cerebellar hemisphere
7. Vermis portion of caudal lobe
8. Paramedian lobule
9. Anisform lobule
(Adapted from de Lahunta, 1983)

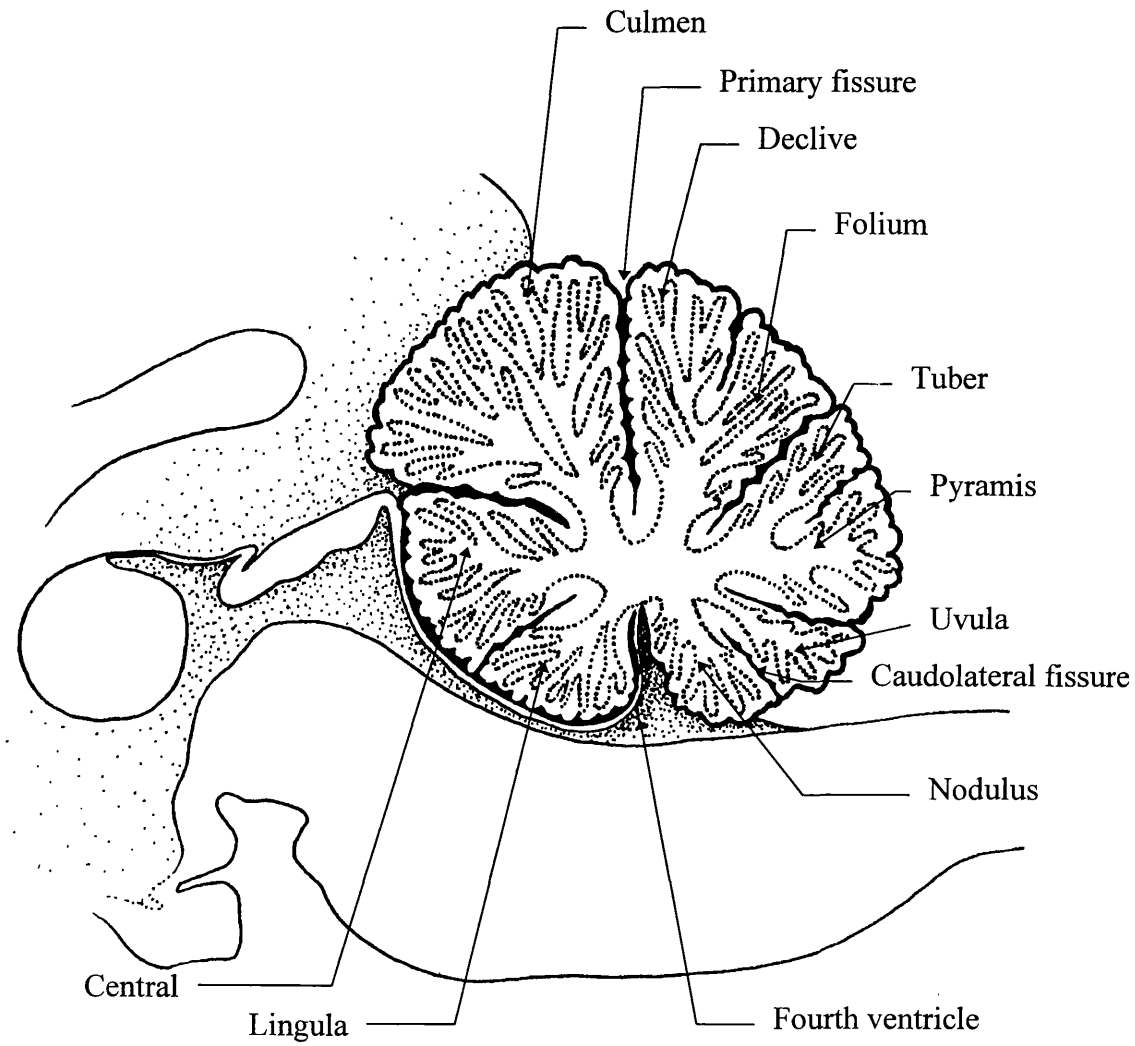

Figure 3. Sagittally transected cerebellum to show the major fissures and lobules. (Adapted from Jenkins, 1978)

Table 1. Anatomical subdivisions and equivalents of descriptive and numeral nomenclature of cerebellar lobules based on the dog (Larsell 1970, Beitz & Fletcher 1993).

		Vermis		Hemisphere	
Fissure	*Lobes*	*D*	*N*	*D*	*N*
	Rostral	Lingula	I	Vinculum lingulae	H I
		Central	II, III	Ala centralis	H II
		Culman	IV, V		H III
				Quadragularis (rostral & caudal)	H IV, V
Primary					
	Caudal	Declive	VI	Simplex	H VI
		Folium	VIIA	Anisformis (rostral crus)	H VII A
		Tuber	VIIB	Anisformis (caudal crus)	H VII B
		Pyramis	VIIIA, B	Paramedianus	H VIII A
				Dorsal paraflocculus	H VIII B
		Uvula	IX	Ventral paraflocculus	H IX
Uvulonodular					
	Flocculonodular	Nodulus	X	Flocculus	H X

D: Descriptive nomenclature

N: Numeral nomenclature

1.2.2 Blood supply and drainage

1.2.2.1 Arterial blood supply to the cerebellum in the dog

The cerebral arterial circle, or the circle of Willis, on the ventral surface of the brain is the collection of systemic arterial blood from incoming branches and several pairs of arteries arise from the circle to supply the brain. The canine cerebral arterial circle is supplied by two main sources, the internal carotid artery and the basilar artery (Nanda 1975).

The basilar artery is formed by joining of the left and right vertebral arteries in the vertebral canal at the level of the origin of the hypoglossal nerve root. It courses rostrally on the ventral surface of the medulla oblongata, trapezoid body and pons; and terminates by joining with the cerebral arterial circle. In the dog, the pattern and origin of the caudal cerebellar arteries is variable and consists of caudal and accessory caudal cerebellar arteries. These vessels may be bilaterally or unilaterally represented. The accessory caudal cerebellar artery arises from the vertebral artery, or the basilar artery, and courses dorsolaterally to the dorsal medulla oblongata. It continues rostrally and ventrally to the vermis to which it is mostly distributed. The caudal cerebellar artery arises from the basilar artery and courses dorsolaterally over the dorsal surface of the medulla oblongata to terminate in the caudal and caudolateral cerebellar hemisphere. It sends anastomosing branches to the middle cerebellar artery and accessory caudal cerebellar artery. In dogs where only the caudal cerebellar artery is present, it supplies the areas otherwise supplied by the accessory caudal cerebellar artery.

The middle cerebellar artery arises from the basilar artery on each side before it reaches the trapezoid body (Nanda 1975). The artery courses laterally and dorsolaterally, passes between the facial and vestibulocochlear nerves and becomes associated with the lateral aspect of the ventral paraflocculus. It terminates by giving branches, to the dorsal and ventral paraflocculus and flocculus, and several perforating branches to the brachium of the pons, vestibular and cochlear nuclei and caudal cerebellar peduncle. It also contributes to the choroid plexus of the fourth ventricle.

The rostral cerebellar artery arises from the cerebral arterial circle and its course is caudally directed. It gives off three terminal branches (lateral, intermediate, medial) which supply the rostral part of the cerebellar hemisphere and vermis. The lateral branch supplies the dorsal and ventral parafloccular lobes rostrolaterally. The intermediate branch is distributed to the anisform lobe and some of the lateral vermis. The medial branch is the direct continuation of the rostral cerebellar artery and supplies the ipsilateral vermis and anastomoses with the similar branch of the other side.

1.2.2.2 Arterial blood supply to the cerebellum in the cat

There are several differences between the cat and dog regarding the blood supply to the cerebellum. Firstly, the cat's brain receives its blood supply from three major sources: anastomotic artery, internal carotid and basilar arteries. Secondly, there are no accessory caudal cerebellar arteries. Thirdly, the caudal cerebellar artery divides into two branches: the caudal branch continues as the caudal cerebellar artery, and the rostral branch continues as the middle cerebellar artery. The rostral cerebellar artery arises as a branch of the mesencephalic artery and its course is similar to that in dogs (Nanda 1975).

1.2.2.3 Drainage of the cerebellum

Drainage of the cerebellum is via the cerebellar veins. They lie in the pia and tend to follow the sulci, and are divided into dorsal and ventral sets (Beitz & Fletcher 1993). The dorsal cerebellar *veins (vv. cerebelli dorsales)* are bilaterally paired and are located in the fissures between the two lateral hemispheres and the central vermis. They receive mainly fine tributaries from the dorsal surface of the cerebellum, and empty into the ipsilateral transverse sinus (Popesko & Ghoshal 1981).

The ventral cerebellar veins (*vv. cerebelli ventrales*) are one or two paired minute vessels, that lie between the lateral hemispheres and the medulla. They drain the ventral surface of the cerebellum as well as the brain stem (Popesko & Ghoshal 1981). However, Beitz & Fletcher (1993) have reported that they mainly drain the brain stem, and empty into the sigmoid or basilar sinuses.

1.2.3 Histology of the cerebellum

1.2.3.1 Cerebellar Grey Matter

1.2.3.1.1 Cerebellar cortex

The cerebellar cortex of mature animals is composed of three distinct layers which are uniform throughout (Figures 4 & 5):

1. a superficial molecular layer (*stratum moleculare*)
2. an intermediate Purkinje cell (*piriform neurone*) layer (*stratum neuronorum piriformium*)
3. a deep granule cell layer (*stratum granulosum*)

The folial surface is covered by leptomeninges, which consists of pia mater and arachnoid mater. The molecular layer has a low cellular density and is composed mostly of dendritic ramifications of the Purkinje cells, axons of the granule neurones, and certain afferent (climbing) fibres from the brain stem. The few cell bodies consist of the more peripheral small stellate cells, and the deeply located basket cells. The basket cells send off axons and collaterals deep to form basket-like networks, which synapse with many Purkinje cell bodies (Jenkins 1978).

The Purkinje cell layer is a single layer of large flask-shaped neurones. The large dendritic arborizations of these cells are in the molecular layer, while the axons pass deeply through the granule cell layer and the medullary core to synapse on the deep cerebellar nuclei (Jenkins 1978). The Purkinje cell axons derived mostly from the flocculonodular lobe project directly to the vestibular nuclei. The main axons of climbing fibres, the dendrites of Golgi and granule neurones, pass through the Purkinje cell layer and enter the molecular layer (de Lahunta 1983).

The granule cell layer is thick and consists of numerous granule cell neurones, the cell bodies of which are small and dark-staining. These cells have little cytoplasm and resemble lymphocytes, giving it a characteristic granular appearance (Jenkins 1978). This layer varies in thickness from 5-6 cells at the bottom to 15-20 cells at the top of a folium (de Lahunta 1983). The granule cell axons course through the Purkinje cell layer into the molecular layer, bifurcate and run parallel with the long axis of the cerebellar folia, intersecting at right angles with the dendritic fields of the Purkinje cells. Among the granule cells in the outer zone of the granule cell layer are Golgi cells. The Golgi cell axons and the mossy fibres synapse on the granule neurones. The main axons of climbing fibres and the Purkinje cell axons pass through the granule neurone layer (de Lahunta 1983).

1.2.3.1.2 Deep cerebellar nuclei

There are 3 pairs of cerebellar nuclei located within the white mater of the cerebellum in the dog and cat. From lateral to medial, they are:

1. Lateral (dentate) nucleus,
2. Interposital nucleus, which is located between the other two nuclei in a transverse plane,
3. Fastigial (medial) nucleus (sometimes known as the roof nucleus, from L. *fastigium*, a roof) lies in the cerebellum immediately dorsal to the fourth ventricle. Phylogenetically, this is the oldest nucleus.

The neurones of the deep cerebellar nuclei receive inhibitory projections from the Purkinje cells, and excitatory projections directly from afferent fibres (i.e. climbing and mossy fibres) entering the cerebellum. King (1987) stated that the net output from the cerebellar nuclei may be either nil or excitatory, but never inhibitory. The output from the cerebellar nuclei depends on the balance between the excitatory influences of the climbing and mossy fibres and the inhibition caused by the Purkinje cells. These influences may cancel each other out and subsequently the neurones of the cerebellar nuclei will not fire; however, if the net balance is positive or excitatory, the neurones of the cerebellar nuclei discharge.

1.2.3.2 Cerebellar White Matter

The cerebellar white matter consists of nerve fibres (i.e. afferent and efferent axons) and glial cells. The nerve fibres enter or leave the cerebellum through the cerebellar peduncles.

1.2.3.2.1 Nerve fibres

Afferent fibres

The afferent fibres are responsible for bringing sensory information into the cerebellum. There are two major types of afferents to the cerebellum: climbing and mossy fibres, which are both excitatory. The climbing fibres originate in the olivary nuclei and enter the cerebellum through the caudal cerebellar peduncle. The main axon projects into the molecular layer and arborizes in synaptic relationship with a Purkinje cell dendritic zone. The collaterals project directly to the neuronal cell bodies of the deep cerebellar nuclei, which are again excitatory (de Lahunta 1983).

The more abundant mossy fibres originate from the pontine nuclei, vestibular nuclei and spinocerebellar tracts and they enter the cerebellum through the middle and caudal cerebellar peduncles. They are so named because of their structural resemblance to moss. Similar to the

climbing fibres, they also send out collaterals which synapse in the deep cerebellar nuclei. The main process terminates by synapsing with the granule cells. The granule cell axons project into the molecular layer, bifurcate to form the parallel fibres that synapse with the dendrites of Purkinje cells (Jenkins 1978). This pathway is again excitatory, although indirectly, to the Purkinje cells.

Efferent fibres

All efferent fibres of the cerebellar cortex are inhibitory except for the granule cells. The Golgi neurones are inhibitory to the granule neurones. Efferents from the granule neurones synapse primarily on Purkinje cells, but also terminate on stellate and basket cells, which, themselves, ultimately project to Purkinje cells (de Lahunta 1983). Thus, the Purkinje cells may be excited or inhibited, depending on the balance between the excitatory influences of climbing fibres, granule cells, and inhibitory influences of stellate and basket cells (King 1987).

The Purkinje cell axon is the only efferent projection from the cerebellar cortex and it is inhibitory. This inhibition is mediated by the neurotransmitter gamma-aminobutyric acid. These axons pass through the granular layer and medullary core of the folium to synapse on the cerebellar nuclei for relay of efferent impulses out of the cerebellum. Some Purkinje cell axons leave the cerebellum directly via the caudal cerebellar peduncle and terminate in the vestibular nuclei (de Lahunta 1983). Efferents of the cerebellar nuclei are facilitory to certain neurones of the brain stem and spinal cord (i.e. the motor command centres of the pyramidal and extrapyramidal systems). In this way, the Purkinje cells of the cerebellar cortex modify function by inhibiting (defacilitating) the output of the cerebellar nuclei.

1.2.3.2.2 Neuroglia in the cerebellum

Neuroglia are separated into macroglia (oligodendrocytes and astrocytes) and microglia (Summers *et al.* 1995).

Oligodendrocytes

Oligodendrocytes have a small cell body and a few to many branched processes which may ensheathe or myelinate CNS axons (Berry & Butt 1997).

Astrocytes

Astrocytes are named for their star-like appearance. Classical studies have identified two main types: the fibrous and protoplasmic astrocytes. The fibrous astrocytes are found predominantly in white matter and have a small soma and long, slender processes. Protoplasmic astrocytes are

found predominantly in grey matter and have numerous short, branched processes radiating from the cell body. Astrocytes contain intermediate filaments which contain a specific glial fibrillary acidic protein (GFAP) which may be identified by immunohistochemical staining using antibodies to GFAP. Their main functions include structural support for the tissue of the CNS, and the formation of a glial limiting membrane over the meninges and parenchymal vasculature. Other functions have been described in detail elsewhere (Berry & Butt 1997). Bergmann glia are a specific type of astrocyte which exist in the cerebellar cortex. Embryologically, these radially arranged glia are thought to form a scaffold and thus guide the migration of neuronal precursors (cited in Berry & Butt 1971). Proliferation of Bergmann astrocytes represents a common finding following hypoxic damage to Purkinje cells (Berry & Butt 1997).

Microglia

Microglia are small elongated bipolar cells with two or three branches. Unlike the glial cells described above, they are of monocytic origin (Perry 1996), i.e. they derive from either monocytes or their precursors in the fetus. In mature CNS, new microglia are thought to be supplied from the endogenous population already present in the brain, and monocytes entering the brain after the fetal period become macrophages. It is generally considered that microglia form a network of antigen-presenting cells in the CNS with primary functions in immune surveillance and inflammation (Berry & Butt 1997).

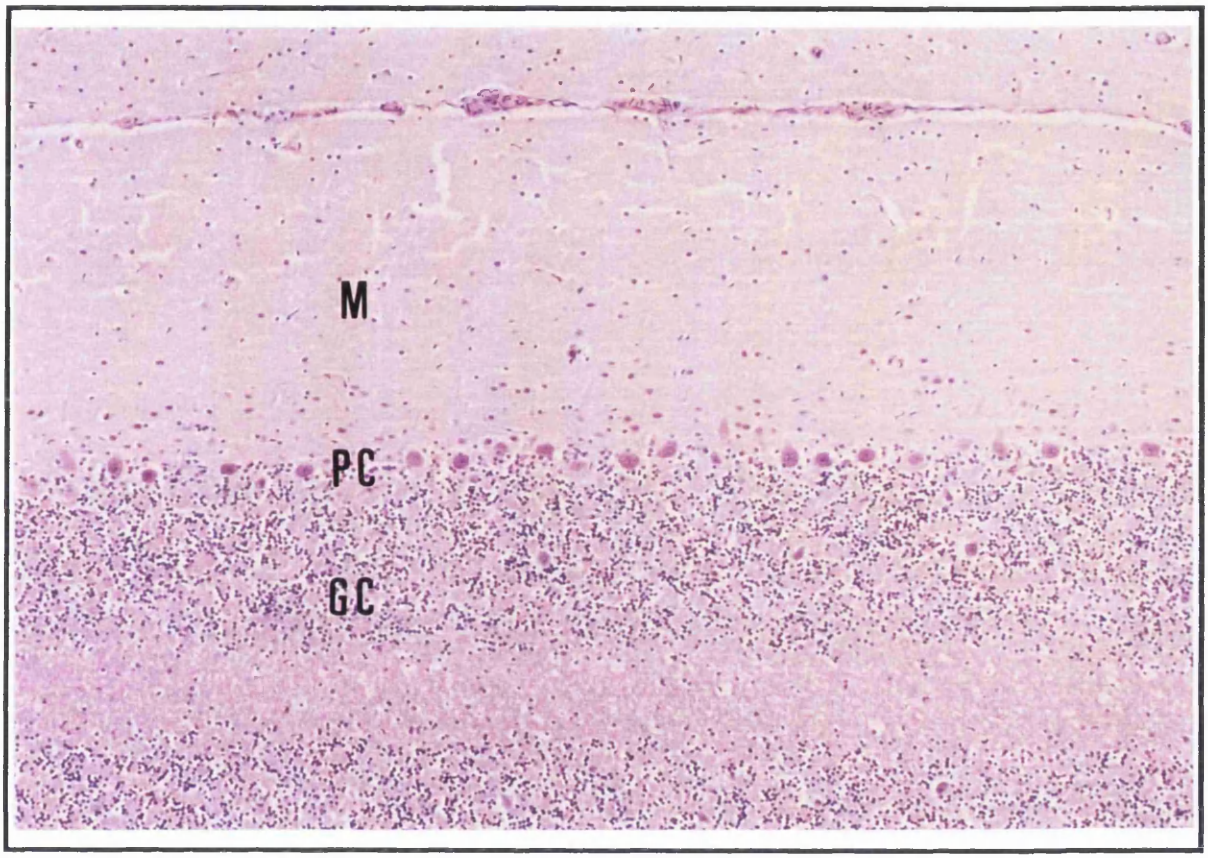

Figure 4.

Histology of the cerebellar cortex showing the molecular (M), Purkinje cell (PC) and granule cell (GC) layers. (H&E, x 110)

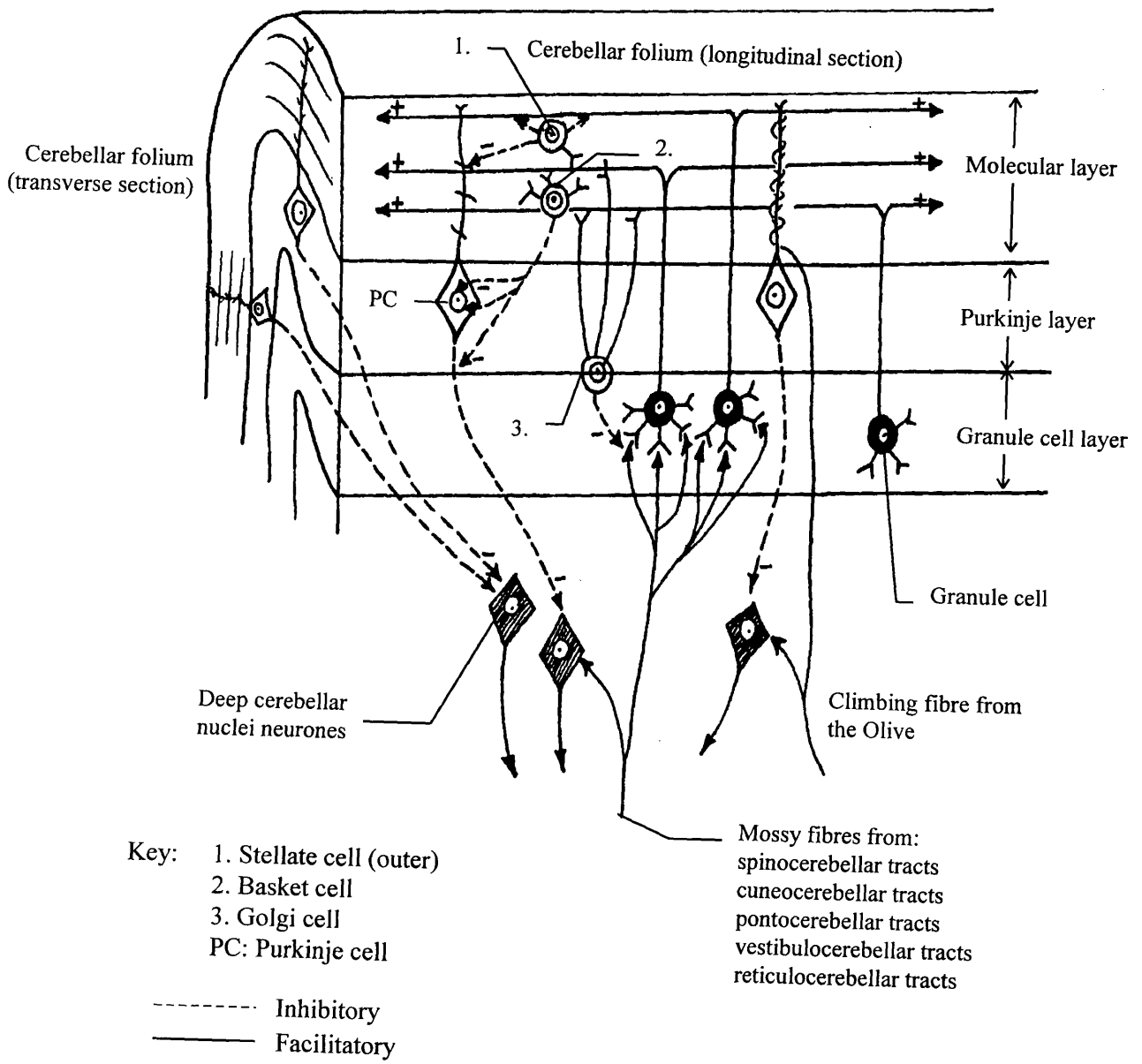

Figure 5. Microscopic anatomy of the cerebellum.

(Adapted from de Lahunta, 1983)

1.2.4 Functional neuroanatomy

1.2.4.1 Cerebellar pathways

1.2.4.1.1 Afferent pathways to the cerebellum

To function as a co-ordinator of muscular activity and regulator of muscle tone, the cerebellum must receive information from the entire body, including proprioception, vestibular and ocular input. It also receives afferents from the upper motor neurone (UMN) system informing it about voluntary activity (de Lahunta 1983).

General proprioception

There are four spinocerebellar tracts transmitting information from the skeletal muscle proprioceptors (muscle spindles and Golgi tendon organ) to the cerebellar cortex (King 1987). They are the dorsal and ventral spinocerebellar tracts from the hind limbs and trunk, the spinocuneocerebellar and cranial spinocerebellar tracts from the fore limbs. These pathways project to the ipsilateral (dorsal spinocerebellar and spinocuneocerebellar tracts) or bilateral (ventral spinocerebellar and cranial spinocerebellar tracts) cerebellar cortex, and the projections are somatotopically arranged. The dorsal spinocerebellar and spinocuneocerebellar tracts enter the cerebellum by the caudal cerebellar peduncle while the ventral spinocerebellar tract reaches the cerebellum by the rostral cerebellar peduncle and the cranial spinocerebellar tract utilises both rostral and caudal cerebellar peduncles (King 1987).

Special senses

Vestibulocerebellar afferents arise in both the vestibular nerve and the vestibular nuclei (Gilman *et* al. 1981). Vestibulocerebellar tracts originating in the vestibular nuclei enter the cerebellum via the caudal cerebellar peduncle and project to the vermis or the adjacent paravermal cortex bilaterally. The projections between the vestibular nuclei and the cerebellum are important in providing the cerebellum with information about balance. Tectocerebellar tracts enter the head area of the vermis by the rostral and middle cerebellar peduncle, informing the cerebellum about visual and auditory status (de Lahunta 1983).

UMN

Pontine nucleus — The corticopontocerebellar pathway originates in the primary motor area of the cerebral cortex, passes through the internal capsule, the crus cerebri, and the longitudinal fibres of the pons. Axons synapse on the ipsilateral pontine nucleus and decussate, forming the

transverse fibres of the pons to enter the contralateral cerebellar cortex via the middle cerebellar peduncle (de Lahunta 1983). This is one of the main pathways by which the cerebral cortex can affect cerebellar neuronal activity (Gilman *et al.* 1981). There is a direct relationship between the evolutionary development of the motor cortex, pons, and cerebellar hemispheres and the degree of skilled motor function (de Lahunta 1983).

Olivary nucleus — Extrapyramidal nuclei of the forebrain and brain stem project information to the contralateral cerebellar cortex, mostly through the olivary nucleus of the medulla oblongata via the caudal cerebellar peduncle. Activated by neurones of the UMN system and spinal cord afferents, the olivary nuclei send off axons (olivocerebellar fibres) which form the source of the climbing fibres to the cerebellum (Jenkins 1978, de Lahunta 1983).

Red nucleus and reticular formation — These extrapyramidal motor centres project to the olivary nucleus, then enter the cerebellum through the caudal cerebellar peduncle, to inform the cerebellum of the intended motor actions (King 1987).

1.2.4.1.2 Efferent pathways from the cerebellum

Purkinje cell axons are the sole output from the cerebellar cortex. Those derived mostly from the flocculonodular lobe, project directly to the vestibular nuclei via the caudal cerebellar peduncle (de Lahunta 1983). The rest of the Purkinje cells project on the deep cerebellar nuclei. The principal efferent fibres from the fastigial nuclei through the caudal cerebellar peduncle are the cerebellovestibular and cerebelloreticular fibres (Jenkins 1978). The fastigial projections to the contralateral vestibular nuclei and reticular formation are called the hook bundle of Russell (Gilman *et al.* 1981).

The cerebellum influences the rubrospinal tract via the interposital nucleus, which sends efferents through the rostral cerebellar peduncle to the contralateral red nucleus. Rubrospinal fibres are sent to influence the flexor motor neurones in the spinal cord (Jenkins 1978). The lateral nucleus also projects through the rostral cerebellar peduncle, to the red nucleus and the pallidum, both have projections to the ventral lateral nucleus of the thalamus, which in turn projects to the cerebral cortex. Another direct feedback circuit to the cerebral cortex exists by direct projection of the lateral nucleus to the contralateral ventral nucleus of the thalamus and the internal capsule (de Lahunta 1983). Efferents of the interposital and lateral nuclei to the reticular formation and efferent feedback pathway from the cerebellar nuclei to the tectum are via the rostral cerebellar peduncle.

The cerebellum has an indirect influence over the lower motor neurone, via its effect on the upper motor neurone tracts that descend into the spinal cord (i.e. vestibulospinal, rubrospinal and reticulospinal tracts) (de Lahunta 1983).

1.2.4.2 Function of the cerebellum

Understanding the function of the cerebellum is important to understand the clinical features of cerebellar dysfunction (Jenkins 1978, de Lahunta 1983, King 1987).

The cerebellum has no primary motor nuclei and no direct fibre connections to the lower motor neurone system, thus it cannot initiate movements. Nevertheless, it functions to co-ordinate and regulate movements initiated by upper motor neurones particularly in the maintenance of equilibrium and in the regulation of tone to preserve the normal posture of the body, both at rest or during motion (Jenkins 1978, de Lahunta 1983).

The cerebellum receives information from the upper motor neurone system concerning the activity being initiated (de Lahunta 1980). It also constantly receives information about muscle proprioception and joint position via spinocerebellar tracts. The cerebellum controls posture by regulating antigravity muscle tone, and uses extra information from the special senses, particularly balance and vision, to achieve normal equilibrium (King 1987). The cerebellum is also involved in the regulation of autonomic reflex function (Beitz & Fletcher 1993). Bradley and Teague (1969) have demonstrated that the pelvic nerve urinary bladder afferent fibres and pudendal nerve afferents from the external urinary sphincter muscle project to the anterior vermis of the cat cerebellum. The experiment indicated that the cerebellum has a tonic depressant effect on the micturition reflex which is organised in the pontine mesencephalic reticular formation.

The cerebellum regulates and co-ordinates movements by comparing response (sensory input) with command (motor output). It can exert pre-control over a movement which is about to take place and also regulate ongoing movements (King 1987). When the motor command centres (e.g. motor centres in the brain stem of dogs and cats) initiate the movement, they inform the cerebellum simultaneously via pontine or olivary nuclei. By means of its feedback projections to the motor centres, the cerebellum can modify, or regulate, the intended movements. A co-ordinated and smooth movement takes place about a joint by contraction of the agonist muscle and simultaneous relaxation of the antagonist muscle. Co-ordination of tone in both the agonist and antagonist muscles is required to fix a joint in position (Jenkins 1978). When a movement begins, the output from stretch receptors of agonists and antagonists is altered and this information is sent to the cerebellum through the spinocerebellar pathways. The cerebellum can

then compare the achieved movement with the planned movement and make appropriate adjustments to the motor systems, affecting rate, range and force of movement. This modification is achieved by altering the level of Purkinje cell inhibition of the deep cerebellar nuclei. Thus, the cerebellum has a vital role in co-ordinating and regulating a single movement, sequential movements and rapidly alternating repetitive movements.

The activities of the cerebellum appeared to be always ipsilateral (King 1987), in contrast to that of the cerebrum. Generally, the right side of the cerebellum receives information from the left motor centres, and the left motor centres initiate movement on the right side of the body. The vestibulo-cerebellar connections are mainly ipsilateral. In addition, the right side of the cerebellum receives major ipsilateral vestibular input and exerts primary control on the right vestibular nuclei. Furthermore, afferents from the spinocerebellar pathways project chiefly to the ipsilateral cerebellum.

1.2.5 Subdivisions of the cerebellum

Several classifications have been used to define the anatomical components of the cerebellum, both in human and veterinary literature. These classifications have been derived from anatomical, phylogenetic, embryological and functional considerations (Gilman *et al.* 1981).

1.2.5.1 Anatomical Organisation

The anatomical organisation of the cerebellum has been described in detail in Section 1.2.1.

1.2.5.2 Comparative anatomical Organisation

The terms archicerebellum, paleocerebellum, and neocerebellum have evolved from phylogenetic and embryologic studies (Gilman *et al.* 1981) (Figure 6).

1. The archicerebellum (Gk. *arche-* primitive, beginning, first) consists of the flocculonodular lobe, which includes the nodulus of the vermis and its lateral floccular appendages. This is the oldest portion phylogenetically, and is confined to the ventral aspect of the cerebellum near its centre.
2. The paleocerebellum (Gk. *palaeos-* old) consists of the vermis of the rostral lobe (culmen, central, lingula) plus the pyramis and uvula of the caudal lobe and paraflocculus.
3. The neocerebellum (Gk. *neos-* new) consists of the lateral portions of the cerebellum and the middle parts of the vermis (declive, folium and tuber lobules).

1.2.5.3 Afferent Organisation

The cerebellum may also be subdivided based on the termination of the major afferent projections (Gilman *et al.* 1981) and correlates with function. The flocculonodular lobe is termed the vestibulocerebellum because the vestibular afferents project heavily to it and it is concerned with vestibular system activity. The vermis is named the spinocerebellum as it receives the major afferent projections from the spinal cord and is thus, mostly concerned with spinal cord function and postural tonus. The projections from the pons terminate in the cerebellar hemispheres, thus, they are called the pontocerebellum which is concerned with regulation of skilled movements. This subdivision matches rather well with the subdivision based on the comparative anatomy, i.e. archicerebellum, paleocerebellum and neocerebellum, respectively. However, many cerebellar afferent projections are not confined to just one of

these regions and it is impossible to divide the cerebellum adequately, solely on the basis of afferent projections.

1.2.5.4 Efferent Organisation — Functional sagittal zones

The cerebellum can be organised functionally into three longitudinally oriented sagittal zones, based upon the organisation of efferent projections from the cerebellar cortex to the deep cerebellar nuclei (corticonuclear projections), and, thus, subdivided into three corticonuclear zones (Jansen & Brodal 1940, Chambers & Sprague 1955 a, b)

Medial zone: consists of the midline cerebellar structures — the vermis and fastigial nucleus are related generally to activities of the midline musculature of the body (Gilman *et al.* 1981). The vermal portion of the cerebellar cortex makes synaptic connections with the fastigial nuclei, which project to vestibular nuclei and the reticular formation in the brainstem. They send ascending projections to the brainstem nuclei (e.g. red nucleus, reticular formation) and descending vestibulospinal and reticulospinal projections to the spinal cord ventral horn cells. Thus, the medial zone is responsible for co-ordinating eye movements, regulating tone, posture, and equilibrium of the entire body.

Intermediate zone: includes the paravermian cortex and interposital nuclei which are involved in functions characteristic of both midline and lateral components (Gilman *et al.* 1981). It regulates spatially organised, skilled movements and adjustments of muscle tone and posture associated with these movements in the ipsilateral limbs. Intermediate portions of the cerebellar cortex have projections to the interpositus nuclei which project to the red nucleus, reticular formation and ventrolateral thalamic nucleus. Many red nucleus neurones contacted by fibres from the interpositus nuclei serve as the origin of the rubrospinal tract, projects to the spinal cord and synapse with ventral horn cells. Thus, the rubrospinal tract affects ventral horn cells related both to proximal and distal limb musculature.

Lateral zone: includes the lateral parts of each hemisphere and the dentate nuclei It is involved in the co-ordination of skilled, spatially organised movements of the extremities, without any apparent regulation of their posture or tone (Chambers & Sprague 1955 b). The lateral portion of the cerebellar cortex is connected to the dentate nuclei which in turn projects to the ventrolateral nucleus of the thalamus. Nerve fibres are then sent into the region of the cerebral cortex involving in limb movement. Thus the lateral hemispheres make connections with a portion of the motor system concerned with finely co-ordinated movements of the extremities (Gilman *et al.* 1981).

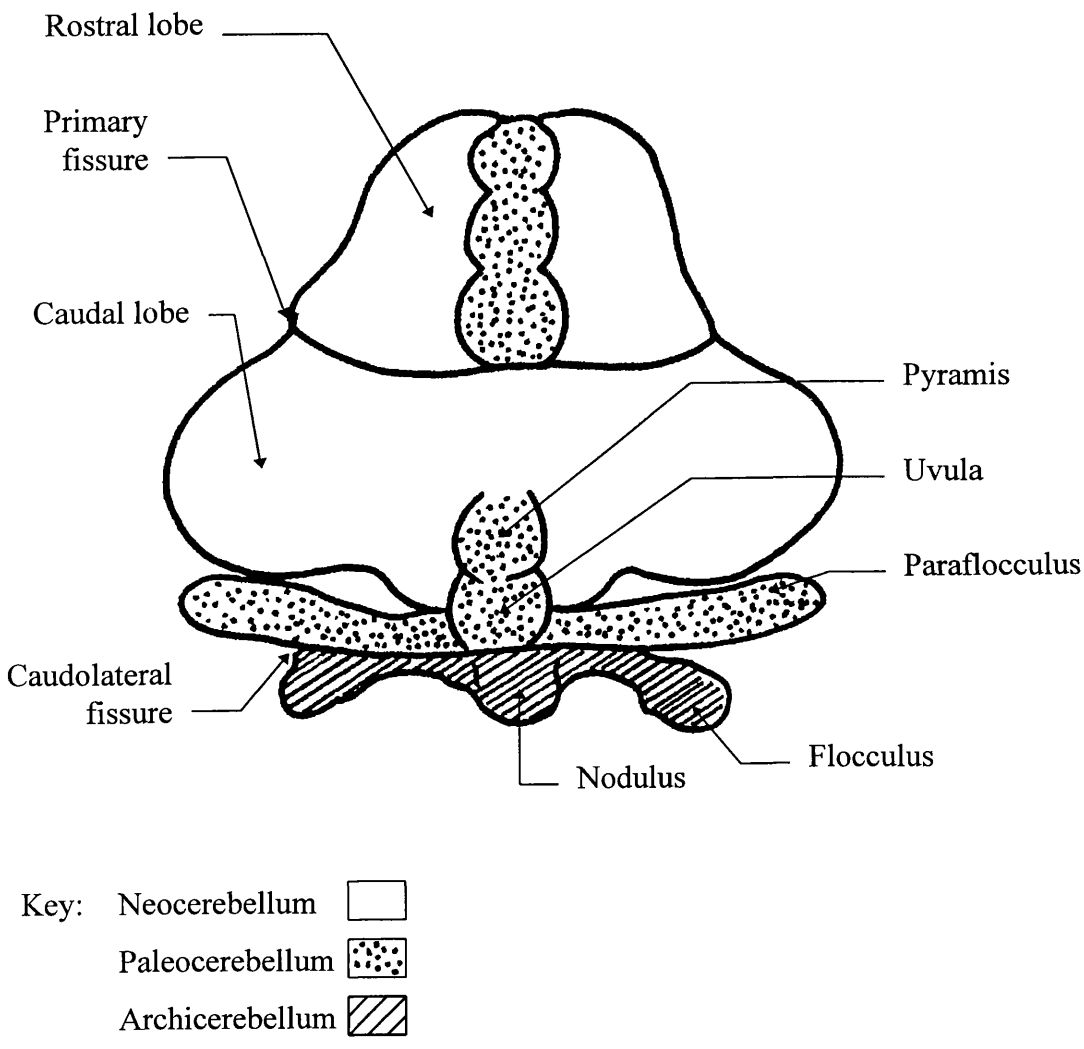

Figure 6. The mammalian cerebellum indicating the major anatomic and phylogenetic divisions. (Adapted from Jenkins, 1978)

1.2.6 Principles of localisation of cerebellar disorders

The relative size and shape of the cerebellum reflects an animal's type of limb movement, centre of gravity, and species posture (Jenkins 1978). From an evolutionary point of view, the cerebellum is small, smooth and unfoliated in cyclostomes and amphibians, but become more prominent in fishes and reptiles, and in birds and mammals the cerebellum is very large, lobed, and convoluted (Hildebrand 1982). The cerebellum of the lower vertebrates (i.e. reptiles, fishes, amphibians) is homologous with the medial portions of the cerebellum of higher vertebrates (mammals), however, the cerebral cortex and portions of the cerebellum homologous with the lateral parts of the cerebellum of higher vertebrates are poorly developed (Gilman *et al.* 1981). Lower vertebrates have adequate neurophysiological mechanisms for controlling posture and gait but only a rudimentary development of finely co-ordinated distal limb movements. Reptiles and birds, which have predominantly trunk-muscle or symmetrical limb movements, generally have a well-developed middle cerebellar portion corresponding to the vermis. In mammals with well-developed limb movements, and especially those with independent limb movements, the cerebellar hemispheres are better developed (Jenkins 1978). In higher primates and humans, the cerebellar hemispheres and the corticopontocerebellar systems are best developed. Particularly increased is the foliation of the cerebellum and the expansion of the lateral hemispheres which permits remarkable developments in the co-ordination of distal limb movements (Gilman *et al.* 1981).

In the CNS, neurones controlling the body musculature generally are represented topographically from medial to lateral corresponding to the musculature (Gilman *et al.* 1981). The same principle can be applied to the cerebellum. It is important to correlate structure and function in the cerebellum, so as to understand its function and dysfunction, and to aid in localising a lesion within the diseased cerebellum. Functional localisation in the cerebellum has been studied in the cat and a somatotopical localisation has been determined by observation of movements produced by stimulation of cerebellar cortex in the decerebrate animal (Figure 7). The body parts are represented in two cerebellar cortical areas, one with the head pointed rostrally and the other with the head pointed caudally (Hampson *et al.* 1952).

The cerebellar cortex can be divided functionally into three bilateral sagittally oriented zones with their related nuclei (See Section 1.2.5.4). In addition, the cerebellum can also be divided on a phylogenetic basis and correlation of structure and function can also be made in this way (See Section 1.2.5.1 & 1.2.5.2).

Based on these principles, a correlation can be made between certain neurological signs and dysfunction of specific portions of the cerebellum. However, these principles of functional localisation are correct only in broad general terms (Gilman *et al.* 1981). Specific point-to-point representations of body parts or discrete physiological functions in the cerebellum apply only to the experimental animal under certain circumstances and are usually not applicable in reality.

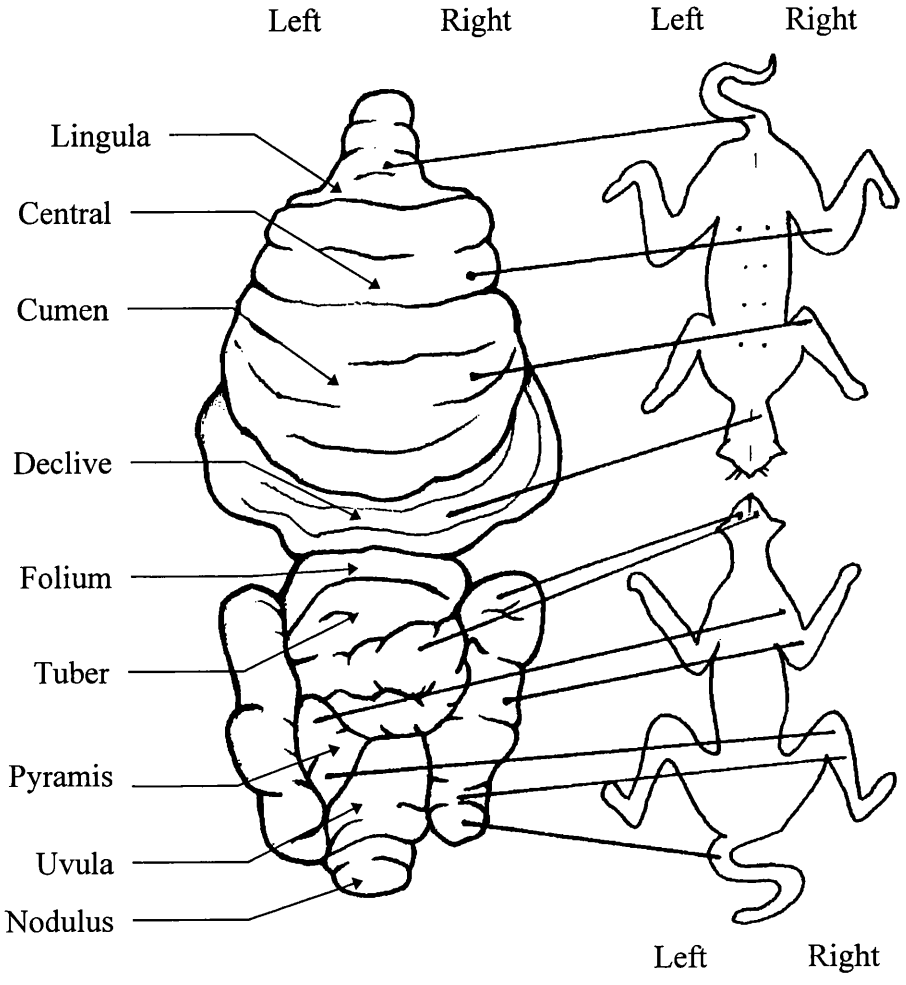

Figure 7. Diagram of the somatotopical localisation in the cerebellum of the cat. (Adapted from Hampson *et al.*, 1952)

1.3 CLINICAL & DIAGNOSTIC FEATURES OF CEREBELLAR DISEASES

1.3.1 General clinical features

The cerebellum is one of the three basic subdivisions of the brain in addition to the cerebrum and brainstem (Beitz & Fletcher 1993). Dysfunction of the cerebellum produces characteristic clinical signs distinct from the other two brain structures. The principle of dysfunction is an inadequate Purkinje cell inhibition of the activity of the deep cerebellar nuclei and vestibular nuclei. Consequently, the animal is incapable of co-ordinating and regulating the normal rate, range and force of voluntary movement, maintenance of normal posture and equilibrium. As a general rule, due to the ipsilateral functioning of the cerebellum, a unilateral lesion produces ipsilateral signs. Diffuse disease processes affecting the cerebellum produce diffuse signs.

In pure cerebellar disease, the animal should have a *normal demeanour* (bright, alert and responsive). There is *no paresis*: the animal's strength is preserved, and *no disturbance of the sensorium* of the animal (de Lahunta 1980 a). However, the ability to co-ordinate, or regulate, muscular activity is altered. The gait is abnormal, characterised by *ataxia*, or inco-ordination, as a consequence of contractions of muscle groups which are irregular in force and direction. The ataxia is worsened with lack of visual input (Coates 1996). The animals may show a *wide-based stance* to overcome the ataxia (Jenkins 1978). Another classical feature of the gait is *dysmetria*, which is an abnormal range, rate and force of movement or the inability to judge distances. This is best observed as an erratic length and height of stride when the animal is walking; and when the animal is attempting to ascend or descend a flight of stairs. Due to inadequate inhibitory function, *hypermetria* is seen rather than hypometria, thus there is an over-measurement in the gait response which is manifested as excessive movement of the limbs in all aspects of motion (de Lahunta 1983). Limb movements typically show a delayed onset of protraction and an exaggerated response. Hypertonia or spasticity may be another major feature of the gait. When the animal is standing or walking, the trunk often sways forward and backward or sideways, or occasionally dorsoventrally, and thus is referred to *truncal ataxia.* This may appear as gross jerky movements of the entire body (de Lahunta 1983). Occasionally, when the animal attempts to move more rapidly, the jerky limb movements become very exaggerated, causing the animal to pitch and fall in any direction and have difficulty remaining on its feet (de Lahunta 1980 a).

While the animal is standing, a fine head tremor may be noted, most noticeable as a tremor of the ear tips and an ocular tremor visible during fundic examination. The tremor is exaggerated by attempted movements because more co-ordination is required. Dysmetria produces an *intention tremor*, which is the uncontrollable involuntary shaky movement, mostly involves the head and extremities as the animal attempts to perform purposeful movements and during the course of movement. The head bobbing or jabbing movements during feeding, or when the animal approaches an object that it intends to smell or pick up, are good examples of intention tremor. When the animal tries to jump off a table, an intention tremor of the entire body can be observed. Sometimes *generalised tremor* may be seen. The tremor may be worsened by excitement. If the animal can be made to look to either side, a fine intention tremor of the eyeball may develop when the eye is fully abducted or adducted (de Lahunta 1980 a). Typically, cerebellar tremors are absent in relaxed or sleep-induced states (Coates 1996).

Resting muscle tone may be increased in animals with cerebellar disease. Hypertonia or spasticity may be noticeable during passive manipulation of the limbs (i.e. during limb flexion and extension). Reflexes range from normal to exaggerated (de Lahunta 1983). Typically postural reactions are slow and show the same delay in onset of protraction and exaggerated responses as observed in the gait. This characteristic is best reflected in the hopping responses. Proprioceptive positioning is usually normal, although the response may be hypermetric. Unconscious proprioception is abnormal, which may be observed as a delayed reflex-stepping response (The latter test consists of a piece of paper being placed under the paw, and the paper is pulled away slowly from the animal's centre of gravity. A normal animal will replace the limb when it is in an inappropriate weight-bearing position).

A rebound phenomenon has been described as a sign of lack of cerebellar control (de Lahunta 1983). This is tested by extending the neck and suddenly withdrawing support. The head, instead of returning to its normal position, may descend ventrally further than normal.

The rostral and vermal portions of the cerebellum are concerned primarily with the inhibition of antigravity or extensor muscle tone of the neck and thoracic limbs. Lesions in this region may result in rigid extension of the thoracic limbs and contraction of the epaxial muscles, producing opisthotonus; while the pelvic limbs may be flexed forward under the body by hypertonia of the hypaxial muscles that flex the hips (de Lahunta 1980 a). Decerebellate rigidity has been observed in experimental animals after ablation of the entire cerebellum, resulting in opisthotonus, tonic extension of the forelimb, alternating clonic movements of the hind limbs, as well as a tendency to stagger and fall backwards if placed on the feet (Holliday 1980).

In animals with extensive cerebellar cortical disease, the menace response will often be reduced or absent. With diffuse cerebellar lesions, menace response is absent bilaterally; and ipsilateral menace deficit in unilateral lesion. Vision is normal (i.e. animal can follow objects visually and does not bump into obstacles), and facial nerve (CN VII) function is normal as tested by the palpebral reflex. For a normal menace response to take place, the entire central visual pathway to the visual cortex (occipital lobe) and CN VII nucleus (in the medulla oblongata) must be intact. An abnormal response observed in the cerebellar patients may be explained by assuming the anatomical pathway between the visual cortex and facial nucleus must pass through the cerebellum. A loss of cerebellar facilitation of cortical activity in the motor area (= inhibitory effect) can prevent the ability of cortical neurones from activating facial neurones for the menace response (de Lahunta 1983). A unilateral cerebellar lesion produces an ipsilateral deficit in the menace response because of the crossing of axons in optic chiasm and pons.

Involvement of vestibular components of the cerebellum (i.e. flocculonodular lobe or fastigial nuclei) may result in vestibular signs. An asymmetrical lesion may result in a head tilt, and nystagmus that is usually apparent only when the head is held flexed to either side (de Lahunta 1980 a). There is variable direction of the positional nystagmus which may change with different positions of the head. The animal may show a loss of equilibrium, a broad-based staggering gait with jerky movements and falling to either side or backwards, especially if the thoracic limbs are elevated. Vestibular disturbances with unilateral lesions of the flocculo-nodular lobe, caudal cerebellar peduncle or cerebellar medulla may produce "paradoxical vestibular syndrome". This term was first used by Palmer *et al.* (1974) to describe lesions contralateral to that expected from the central vestibular signs. Vestibular function is determined by the relative firing rates of neurones in the vestibular nuclei. Neurones in the flocculus travel via the caudal cerebellar peduncle and normally inhibit the ipsilateral vestibular nuclei. Lesions in this pathway results in loss of inhibition, thus, increased firing of neurones in the ipsilateral vestibular nuclei. This causes the same signs as decreased firing of the contralateral vestibular nuclei, and results in contralateral vestibular signs. Classical clinical signs include ipsilateral postural reaction deficits (i.e. hemiparesis, proprioceptive deficits) with cerebellar signs on the same side of the lesion (i.e. ataxia, hypermetria, abnormal menace response), and contralateral vestibular signs (i.e. head tilt, leaning and circling, nystagmus). The syndrome is usually caused by a destructive, mass-occupying lesion.

Jenkins (1978) and King (1987) correlated cerebellar lesions with the symptomatology based on the phylogenetic division and afferent organisation of the cerebellum, respectively. Jenkins (1978) described specific syndromes corresponding to lesions affecting the archicerebellum,

paleocerebellum and neocerebellum. King (1987) has described vestibulocerebellar, ponto-cerebellar and spinocerebellar syndromes. In veterinary practice, however, an animal is seldom presented at such an early stage that the lesion is still restricted to only one of the three functional regions of the cerebellum. As initial signs are often subtle, the animal is usually presented with a combination of the three basic syndromes.

The cerebellum normally has an inhibitory influence on urination by inhibiting the detrusor reflex (See Section 1.2.4.2). Rarely, a cerebellar lesion results in frequent urination due to loss of inhibition or detrusor hyperreflexia (Oliver & Lorenz 1993). Cerebellar hypoplasia may result in frequent, precipitous voiding with a reduced bladder capacity (Oliver & Selcer 1974).

1.3.2 Ancillary diagnostic techniques

The signalment and history are important in the evaluation of cases of cerebellar diseases. Breed and pedigree information may suggest a familial or hereditary disorder. The age of onset and progression of the disease will provide important information about the nature of the disease. The clinical findings reflect whether the disease is lateralised, focal or diffuse in nature, and whether the disease is confined to the cerebellum or involves other parts of the CNS and/or other body systems. One may be able to draw up a list of differential diagnoses from the signalment, history, clinical and neurological examination but rarely can one make a definitive diagnosis from them. Thus, further investigation is usually carried out to evaluate the underlying cause of the problem. A general overview of the techniques which may be utilised for the investigation of cerebellar disease and the relevant information which they may provide is given as follows.

1.3.2.1 Clinical pathology

Complete blood count and biochemistry are useful in detecting underlying disorders such as systemic infection/inflammation or metabolic disease which may affect the cerebellum. However, most cerebellar diseases are rarely associated with changes in the peripheral blood. Haematology and biochemistry are usually indicated as a routine procedure prior to general anaesthesia and cerebrospinal fluid tap.

Serological examination may provide evidence of infection such as feline infectious peritonitis virus (FIPV), feline immunodeficiency virus (FIV), feline leukaemia virus (FeLV), canine distemper virus (CDV), *Toxoplasma gondii* and *Neospora caninum*, especially when the animal is showing diffuse cerebellar signs. Enzyme assay of white blood cell, serum, plasma, skin

fibroblast in tissue culture can be performed if lysosomal storage disease (LSD) is suspected (Wood 1995). Screening urine for intermediate molecules of metabolism may identify a LSD or intermediary metabolic disorder.

1.3.2.2 Cerebrospinal Fluid Analysis

Cerebrospinal fluid (CSF) analysis is indicated whenever a CNS disease is suspected. It is the most reliable antemortem diagnostic test available to determine the presence of lesions that do not alter gross brain structure (Bagley 1996), especially in identifying CNS inflammation (Muñana 1996). It may be useful in evaluating patients suspected of having an intracranial neoplasm (Nafe 1990). If cerebellar disease is suspected, a CSF sample is collected from the cisterna magna under general anaesthesia. Methods of collection and analysis of CSF are detailed in the literature (Mayhew & Beal 1980, Kornegay 1981, Cook & DeNicola 1988, Kornegay 1991 a, Evans 1992, Rusbridge 1997 a). Generally, a total white blood cell count, differential cytology and protein concentration of CSF provide the most important information. However, lesions which do not communicate with the CSF pathway will not influence CSF composition (Nafe 1990). Examples of this may include parenchymal inflammatory lesions or neoplasms which are located deeply in the cerebellum. The earlier in the course of the brain neoplasia the CSF is evaluated, the greater the chance of a normal result (Bailey & Higgins 1986 a). Thus, a normal CSF sample does not rule out a particular disease.

CSF collection is contraindicated in animals with clinical signs suggesting raised intracranial pressure (i.e. mental depression, disorientation, stupor, coma or papilloedema). Cerebellar neoplasia, inflammation, or intracranial haemorrhage or oedema often cause increased intracranial pressure. Brain herniation, in particular, cerebellar herniation through the cisterna magna may result from sudden release of pressure at the time of CSF collection.

Pleiocytosis is often observed in CNS inflammation, and the differential white blood cell count may provide information regarding the nature of the inflammatory process (Vandevelde & Spano 1977, Muñana 1996). CSF protein concentration may be increased due to breakdown of the blood-brain barrier, and/or intrathecal immunoglobulin production. Agarose electrophoresis of CSF has been shown to correlate with clinical and pathologic conditions and may aid in diagnosis of CNS disorders (Sorjonen 1987). Cultures and titres performed on the serum and CSF may identify an infectious cause. CSF analysis is seldom diagnostic for intracranial neoplasms because seldom do these tumours exfoliate cells into the CSF (Moore *et al.* 1996). Nevertheless, choroid plexus tumour cells may shed into the CSF. A marked elevation in CSF protein concentration without a concomitant increase in white cell numbers is generally

considered to be suggestive of brain tumours albeit this is not pathognomonic and may be seen in other cerebrovascular or inflammatory diseases. Pleiocytosis may occur due to tumour-associated inflammation. It has been shown that high CSF white cell counts and protein concentrations are indicative of neurologic disease, despite moderate iatrogenic blood contamination (Hurtt & Smith 1997). Characteristic CSF findings will be covered separately in Section 1.6 on cerebellar diseases.

1.3.2.3 Diagnostic Imaging

1.3.2.3.1 Radiology

Survey radiography of the skull often does not contribute significant diagnostic information for intracranial disease, except for detecting hydrocephalus, structural deformities such as cranial fractures, malformation of the calvarium, cortical thinning, persistent fontanelles, or demonstration of osteolytic or osteoproductive lesions. Some mineralised brain tumours or granulomatous lesions may be recognised on high-detail radiographs (Tucker & Gavin 1996). Hyperostosis of the calvarium may occur in meningiomas (Moore *et al.* 1996) so that this may be visualised on plain radiography. Thoracic radiographs (preferably inflated chest bilaterally) may also demonstrate pulmonary metastatic tumours.

1.3.2.3.2 Ultrasonography

The ultrasonographic anatomy of the normal canine brain has been described (Hudson *et al.* 1989) and the cerebellum is one of the intracranial structures identified using B-mode ultrasound. Ultrasound imaging can be performed through the fontanelles in neonatal animals, in older animals with persistent fontanelles or by craniotomy in animals lacking fontanelles (Tucker & Gavin 1996). Transcranial doppler imaging may be useful for evaluating intracranial vasculature structures. Intraoperative sonography can be used in animals to guide needle placement for brain biopsy and to assist with resection of brain lesions (Thomas *et al.* 1993 a, Penninck 1995, Nyland *et al.* 1995).

1.3.2.3.3 Magnetic Resonance Imaging & Computed Tomography

Magnetic resonance imaging (MRI) and computed tomography (CT) are non-invasive imaging techniques which are useful in the diagnosis of intracranial lesions, especially those that alter the structural integrity of the brain tissue (Bagley 1996), for instance, neoplasms. The principles of how MRI and CT obtain an image have been described elsewhere (Kornegay 1990 a, Thomson *et al.* 1993, Tucker & Gavin 1996).

In general, the image obtained by MRI is superior in anatomical detail and more informative than that obtained by CT because of its high resolution and soft tissue contrast. The cerebellum, situated in the caudal fossa, is better visualised using MRI, because bony tissue does not interfere with MRI, while the caudal fossa is obscured by the petrous temporal bone and is difficult to image with CT (Panciera *et al.* 1987). CT is preferable for visualising lesions causing bone lysis or calcification. Further enhancement of the contrast between normal and abnormal tissues can be accomplished with an intravenous injection of iodinated contrast agents during imaging (Tucker & Gavin 1996). Since different lesions have characteristic patterns of enhancement, a more accurate diagnosis can be made based on imaging. The characteristics of different lesions have been described in details elsewhere (LeCouteur *et al.* 1981, 1983, Turrel *et al.* 1986, Kornegay 1990 a, Thomas *et al.* 1993 a, Thomson *et al.* 1993, Tucker & Gavin 1996). The recent development of three-dimensional CT demonstrates the exact location and extent of intracranial lesions in relation to adjacent normal structures. This aids planning of approaches for surgery and radiation therapy (Tucker & Gavin 1996). CT-guided stereotactic brain biopsy has been performed in cats to provide accurate diagnosis of a variety of neoplastic and non-neoplastic brain lesions (LeCouteur *et al.* 1999).

MRI is superior for localising CNS infections or inflammation, and has been used to detect demyelinating diseases (Thomson *et al.* 1996). Thomson *et al.* (1996) have utilised MRI to identify congenital anomalies such as cerebellar hypoplasia in cats, and for the diagnosis and monitoring of dogs with infarctions.

1.3.2.3.4 Neuroscintigraphy

Brain scintigraphy provides useful anatomical and functional information such as cerebral blood flow and cerebral metabolism, although CT and MRI provide superior morphological detail of the brain (Daniel *et al.* 1992). Conventional brain scintigraphy still has a place in veterinary medicine especially if CT or MRI is not available. New tomographic neuroscintigraphy such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) have been developed recently, and by use of new classes of radiopharmaceuticals which cross the blood-brain-barrier, the perfusion status of the brain can be evaluated (Tucker & Gavin 1996). PET is commonly used to image the physiological and biochemical activity of brain tissue in humans. It has been used to assess dementia, epilepsy, tumours, degenerative diseases, and cerebral vascular lesions. Nonetheless, the expense limits its use in veterinary medicine except for collaborative research.

1.3.2.4 Histopathological Examination

CSF analysis and advanced diagnostic imaging may provide useful information to achieve an antemortem diagnosis, however, in many cases, CSF examination may be normal, or MRI/CT may not clearly differentiate neoplastic diseases from inflammatory or vascular diseases. Histopathologic examination is generally required for definitive diagnosis. Ultrasound-guided or CT-guided stereotactic brain biopsy can be utilised to obtain biopsy specimens from the cerebellum for histological examination. Craniotomy and biopsy of the cerebellum may provide a better specimen.

The definitive diagnosis of most neurodegenerative diseases generally requires post-mortem histopathological examination. However, the histopathology often does not correlate with clinical signs of progressive neurologic deterioration (March 1996) indicating inadequate understanding of the pathogenic mechanisms in these disorders.

A thorough understanding of the normal histology of the cerebellum is prerequisite to appreciate the abnormal microscopic appearance in cerebellar diseases. There is a wide variety of staining techniques used for cerebellum, routine staining with hematoxylin and eosin (H&E) and cresyl violet usually provide adequate evaluation. Further inspection of particular tissue element within the cerebellum may require special staining techniques (Summers *et al.* 1995). For example, Calbindin-D-28K immunoreactivity can be utilised as a specific marker for Purkinje cells as Calbindin-D-28K is an intracellular calcium-binding protein expressed in Purkinje cell bodies and processes (Yan & Garey 1998); astroglial cells can be demonstrated by immunoperoxidase staining for GFAP; phosphorylated and non-phosphorylated forms of neurofilament protein can be labelled by SMI 31 and SMI 32, respectively.

Electron microscopic examination of cerebellar tissue may provide ultrastructural information which the light microscopic examination cannot provide or when changes are subtle at the light microscopic level.

1.4 BASIC PATHOLOGICAL REACTIONS IN THE CEREBELLUM

A wide variety of pathological processes may occur in the cerebellum. Some of these can be detected grossly while others are only noted microscopically. A basic understanding of these processes is essential to aid histopathological diagnosis. In this section, only basic pathological processes of the cerebellum are discussed (Kornegay 1990 b).

1.4.1 Hypoplasia

Hypoplasia indicates the failure of an organ to develop to its full size. Intrinsic (inherited disorder) or extrinsic (e.g. *in utero* viral infection, teratogens, nutritional deficiencies) insults may have a profound effect on the developing cerebellum, depending upon the stage of embryonic development at which they act. These processes may affect the normal development of the germinal populations of neuroepithelial cells, or cause degeneration and necrosis of germinal cells. Alternatively, the cerebellum may fail to differentiate properly. The cerebellum can be uniformly affected or specific lobes or areas may be selectively involved. Microscopically, differentiated portions may be normal or variable lesions may be detectable. Specific cerebellar neurones may be absent, reduced in number or displaced from their normal anatomic position. The latter neurones are described as being ectopic or heterotopic (de Lahunta 1983, Kornegay 1990 b). Extensive cerebellar cortical hypoplasia, or degeneration, often results in associated shrinkage of the middle cerebellar peduncle, decrease in size of transverse fibres of the pons and pontine nuclei (Summers *et al.* 1995).

1.4.2 Atrophy

Atrophy is an acquired overall reduction in tissue mass, and is due to destruction of an already differentiated (neuronal) population. Cerebellar atrophy may result from necrosis, subsequent to lesions such as infection or infarction. Several inherited, degenerative cerebellar diseases may result in atrophy, for example, cerebellar abiotrophy (Summers *et al.* 1995).

1.4.3 Abiotrophy

Abiotrophy refers to the lack (a-) of a vital (bios-) substance necessary for the nutritional (-trophy) life of that cell (de Lahunta 1983). It indicates a degeneration due to an intrinsic abnormality in the metabolic functioning of the neurone that does not permit its survival. The

cerebellum is affected after its cellular component has developed fully (Summers *et al.* 1995). Cerebellar abiotrophies principally affect Purkinje and granule cells, although other neuronal systems can be affected since abiotrophy is usually a multineuronal disorder. Purkinje cells are usually first affected and are reduced in number or even depleted. In an ongoing degeneration and loss of Purkinje cells, empty baskets, multifocal gliosis at the interface of the granular and molecular layers (Bergmann's gliosis) and the presence of torpedoes (spheroids of Purkinje cell axons) may be evident in the granule cell layer, cerebellar white matter, or the nuclei of the cerebellar medulla. Wallerian degeneration may also be found in the white matter of the folia subsequent to Purkinje cell degeneration (Summers *et al.* 1995). The pathogenesis of abiotrophy is still poorly understood.

1.4.4 Transsynaptic neuronal degeneration

Neurones function by generating membrane action potentials that are conducted as an electrical impulse for the length of the axon. At the synapse, this electrical signal is converted into a chemical signal that cross the synaptic cleft to stimulate the next neurone. Thus a single neurone is a link in a chain, and the loss of any neurone has consequences for the chain as a whole (Summers *et al.* 1995). Secondary degeneration of neurones which project to, or from, primary degenerated neurones is referred to as transsynaptic neuronal degeneration. There are two forms of transsynaptic neuronal degeneration (Kornegay 1990 b). In anterograde degeneration, neurones receiving input from the primarily affected cell degenerate. Retrograde degeneration implies degeneration of neurones that project to the primarily affected neurone. A primary Purkinje cell lesion may lead to anterograde transsynaptic degeneration in the deep cerebellar nuclei and retrograde transsynaptic degeneration in the olivary nuclei. In animals, however, transsynaptic neuronal degeneration is lacking in most cerebellar abiotrophies, in contrast to comparable human disorders (Summers *et al.* 1995).

1.5 CLASSIFICATION OF CEREBELLAR DISEASES

Diseases affecting the cerebellum can be classified in different methods to facilitate an accurate diagnosis, prognosis and institute appropriate treatment. Kornegay (1985) classified cerebellar diseases according to whether the lesions are static, progressive, or reversible. Static diseases include cerebellar hypoplasia and cerebellar dysplasia; progressive diseases include encephalitides, LSD, cerebellar cortical abiotrophies and neoplasia; reversible diseases include dysmyelinogenesis.

De Lahunta (1983) classified cerebellar diseases into two broad categories: congenital and acquired diseases. The congenital cerebellar diseases are those in which the abnormality has occurred during gestation or prior to normal ambulation, which can be further divided into neonatal syndromes and postnatal syndromes (de Lahunta 1980 b, Oliver & Lorenz 1993). The former indicates that the clinical signs are present at birth which includes viral infection, malformation, hypomyelinogenesis-dysmyelinogenesis and abiotrophy. The latter indicates that the onset of signs is after birth but reflects a proven or presumed inherited deficit in cell metabolism, which includes abiotrophy and storage disease. Acquired cerebellar diseases include inflammations, neoplasms, diffuse degenerations (intoxications) and injury.

The DAMNIT system has been used by Oliver and Lorenz (1993) and Braund (1994) to categorise cerebellar diseases based on the aetiologies. The category includes degenerative, developmental, neoplastic, inflammatory or infectious, idiopathic, traumatic, toxic and vascular diseases. The above authors also further differentiate cerebellar diseases into groups according to acute or chronic onset and whether the diseases are progressive or non-progressive. A similar system has also been used by Summers *et al.* (1995) to classify nervous system diseases based on pathology.

1.6 CEREBELLAR DISEASES IN DOGS & CATS (DAMNIT SYSTEM)

The cerebellum is susceptible to a variety of diseases. In view of this, the present study makes use of the DAMNIT system with modification, by grouping 'vascular diseases' (previously grouped in an additional 'V') as 'angiopathies' (belongs to 'A'). In addition, cerebellar diseases are not further classified based on their onset or progression because the presentation of cerebellar diseases varies and overlapping occurs in many circumstances. The modified DAMNIT classification includes thirteen groups of diseases, which are: degenerative, angiopathic, anomalous, metabolic, neoplastic, nutritional, iatrogenic, idiopathic, immune-mediated, infectious, inflammatory, toxic and traumatic diseases. The main aetiologies of cerebellar disease are listed in Table 2. The author finds this an extremely useful tool to categorise diseases and help in developing a list of differential diagnoses.

This section reviews recognised primary disorders of the cerebellum and conditions which involve the cerebellum secondarily. Specific clinical, diagnostic and pathological features are reviewed as well as treatment options if available, and prognosis.

Table 2. Main aetiologies of cerebellar disease in dogs and cats

D	Degenerative	Abiotrophies Lysosomal storage diseases
A	Angiopathic	Infarction Embolism Haemorrhage
A	Anomalous	Developmental or congenital cerebellar anomalies
M	Metabolic	Intermediary metabolism disorders
N	Neoplastic	Medulloblastoma Meningioma Glioma Choroid plexus papilloma Intracranial epithelial cyst Metastatic neoplasms
N	Nutritional	Thiamine deficiency
I	Infectious	Viral diseases Protozoal Rickettsial Fungal Parasitic Feline spongiform encephalopathy (FSE)
I	Inflammatory/ idiopathic/ immune-mediated	Granulomatous meningoencephalomyelitis (GME) Steroid-responsive tremor syndrome (idiopathic cerebellitis)
T	Toxic	Lead, organophosphates, plants etc.
T	Traumatic	Head injury, cerebellar herniation

1.6.1 Degenerative cerebellar diseases

This section will focus on degenerative cerebellar disease due to inherited causes. Toxic or nutritional causes may also lead to degenerative brain disorders (March 1996). Clinical features of these degenerative diseases are apparent lack of abnormality at birth followed by onset of progressive neurologic signs later in life. Age of onset, speed of progression and clinical presentation vary among different diseases, species and breeds, and clinical heterogeneity sometimes occurs in different individuals with the same disease (March 1996). The prevalence of cerebellar signs early in the disease course is a consistent feature, albeit other CNS signs may be present concomitantly or develop as the disease progresses.

1.6.1.1 Lysosomal storage diseases

LSD are a group of inherited diseases resulting from a mutation or deletion in a gene encoding a lysosomal enzyme or an activator protein needed for *in vivo* enzyme activities (Wood 1995, Summers *et al.* 1995). The hydrolytic enzymes are contained in intracellular organelles called lysosomes. If the activity of one or more of these enzymes are deficient, undegraded metabolites accumulate intracellularly, resulting in cell dysfunction and cell death eventually. Although the defect is present in all cells of the body, many manifest as neurologic disorders (de Lahunta 1980 a). It is because neurones are post-mitotic, permanent cell populations and are rich in specific glycolipids (e.g. plasmalemmal ganglioside), which makes them prone to specific enzyme deficiencies (Summers *et al.* 1995). LSD may affect neurones or white matter preferentially, causing neuronal storage diseases and leukodystrophies, respectively. Most LSDs are inherited as autosomal recessive traits (Hoskins 1995) and X-linked traits (Wood 1995).

Although LSD are multisystemic diseases in dogs and cats, cerebellar signs predominate throughout the clinical course in many cases (March 1996). Concomitant cerebral and brain stem signs are often evident later in the disease course but are rarely the primary presenting problem. Dogs and cats with different LSD types presented with predominantly cerebellar dysfunction are summarised as Table 3. Other LSD are well documented (Summers *et al.* 1995, March 1996, Jolly & Walkley 1997).

Clinical signs may be of acute or gradual onset, usually noticed within the first few weeks or months of life though animals may show signs later in life. The clinical signs are, with no exception, progressive. LSD should be suspected in dogs and cats with progressive diffuse cerebellar signs or with signs of multifocal neurologic involvement. Other common

inflammatory CNS disorders (i.e. meningioencephalitis secondary to other diseases) should be ruled out first by performing CSF analysis. Urine screening for intermediate metabolites may be useful in identifying specific LSD. Histological examination of skin or liver biopsy may demonstrate characteristic storage materials intracellularly and provide a diagnosis. A definitive diagnosis is made through quantitation of the deficient enzyme in white blood cells, plasma, serum, cultured skin fibroblasts and other tissues (Wood 1995). Post-mortem diagnosis is achieved through histopathologic examination (light and electron microscopy) utilising special staining methods, enzyme analysis of frozen tissues, extraction and analysis of stored metabolites.

Treatment of LSD is very limited. Supplementation of the defective enzyme exogenously may be accomplished through infusion of the enzyme (where lysosomal storage primarily affects the reticuloendothelial system), or bone marrow transplantation (Jolly & Walkley 1997). Recent research has been focused on gene therapy (Sly & Vogler 1997). Control and prevention of the disease is to recognise heterozygotes and eliminate them from the breeding group (Wood 1995).

Table 3. Lysosomal storage diseases reported in dogs and cats with cerebellar signs

Disease	Deficient Enzyme	Breeds affected*	Clinical signs	References
GM1 gangliosidosis	β-galactosidase Type I & II	Domestic shorthair (2-3 m, Type I, II) Siamese (2-3 m, Type II) Korat (7 m, Type II) Beagle cross (5 m, Type I, II) English Springer Spaniels (4 m, Type I) Portuguese Water dogs (4-6 m, Type I, II)	Ataxia, dysmetria, tremor, truncal sway, corneal opacities, visual deficits, nystagmus, dysphagia, tetraparesis, skeletal deformities, dementia, exaggerated acoustimotor response, seizures, hepatomegaly (Type I: Facial dysmorphia, skeletal deformities, hepatomegaly Type II: delayed onset CNS dysfunction, no skeletal abnormalities, mild visceral involvement)	Alroy *et al.* 1985 Baker *et al.* 1976, 1979 Barker *et al.* 1986 De Maria R *et al.* 1998 Dial *et al.* 1994 Murray *et al.* 1977 Read *et al.*1976 Rodriguez *et al.* 1982 Shell *et al.* 1989
GM2 gangliosidosis	β-hexosaminidase (A,B) (B-variant form: Hex-A O-variant form: Hex-A,B AB-variant: activator protein)	Domestic shorthair (4-10 w, O-variant) Korat (4-7 w, O-variant) German Shorthaired Pointers (6-9 m) Japanese Spaniel (18 m, AB variant) Mixed breed (1.5 y, O-variant)	Ataxia, tremor, intention tremor, hypermetria, paresis, facial deformities, myoclonus, corneal opacities, blindness, seizures, dysphagia, hepatomegaly	Baker *et al.* 1976, 1979 Cork *et al.* 1977 Cummings *et al.* 1985 Karbe 1973 Neuwelt *et al.* 1985
Globoid cell leukodystrophy (Galactocerebrosidosis)	β-galactocerebrosidase	Domestic Shorthair (5-6 w) Basset Hound (2.5 y) Beagle (4 m) Bluetick Hound (4 m) Cairn Terrier (2-5 m) Miniature Poodle (2 m) Pomeranian (3.5 m) West Highland White Terrier (3-5 m)	Ataxia, tremor, intention tremor, dysmetria, tetraparesis, postural deficits, urinary and faecal incontinence, blindness, nystagmus, dementia	Boysen *et al.* 1974 Fletcher *et al.* 1966 Howell & Palmer 1971 Johnson 1970 Johnson *et al.* 1975 Luttgen *et al.* 1983 Selcer & Selcer 1984 Zaki & Kay 1973
Glucocerebrosidosis	β-glucosidase	Sydney Silky Terriers (7 m)	Ataxia, hypermetria, tremor, hyperactivity, exaggerated segmental reflexes	Hartley & Blakemore 1973
Galactosialidosis	β-galactosidase & α-neuraminidase	Schipperke dog (4 y)	Ataxia, incoordination, hypermetria, nystagmus, exaggerated segmental reflexes	Knowles *et al.* 1993

Sphingomyelinosis	Sphingomyelinase	Balinese (4 m, type A) Domestic Shorthair (2-4 m, type C) Siamese (3-4 m, type A) Miniature Poodle (5 m, type A) Boxer (2 m, type C)	(Type A) Tremor, hypermetria, para/tetraparesis, stunted, hepatomegaly, stereotypical chewing behaviour (Type C) Intention tremor, ataxia, dysmetria, decreased menace response, hepatomegaly	Baker *et al.* 1987 Brown et al 1994 Bundza *et al.* 1979 Chrisp *et al.* 1970 Kuwamura *et al.* 1993 Lowenthal *et al.* 1990 Muñana *et al.* 1994 Wenger *et al.* 1980
Mannosidosis	α-mannosidase	Domestic Longhair (since ambulatory) Domestic Shorthair (4-7 m) Persian (8 w-2 m)	Ataxia, tremor, intention tremor, dysmetria, opistotonus, nystagmus, skeletal defects, generalised weakness, emaciation, paraparesis, hepatomegaly	Blakemore 1986 Cummings *et al.* 1988 Jezyk *et al.* 1986 Maenhout *et al.* 1988 Vandevelde *et al.* 1988
Fucosidosis	α-L-fucosidase	English Springer Spaniel (6-12 m)	Ataxia, hypermetria, behaviour & temperament change, visual impairment/ blindness, proprioceptive deficits, deafness, nystagmus, jaw champing, enlarged peripheral nerves	Barker *et al.* 1988 Herrtage 1988 Keller & Lamarre 1992
Ceroid Lipofuscinosis	Unknown, perhaps p-phenylenediamine	Siamese cats (2-7 y) Domestic Shorthaired cats (7 m) Australian Cattle dogs (12 m), Border Collies (15-23 m), Chihuahuas (13-21 m), Cocker Spaniel (1.5-6 y), Corgi (6-8 y), Dachshunds (3-6 y), Dalmations (6 m), English Setters (12-18 m), Golden Retriever (16-18 m), Miniature Schnauzer (2-3 y), Terrier cross (4 m), Tibetan Terrier (3-6 y), Salukis (12 m), Spitz (19 m)	Visual deficits/ nyctalopia or blindness, behaviour changes, pelvic limb stiffness, ataxia, tremor, intention tremor, hypermetria, dementia, jaw-champing episodes, seizures, nystagmus, proprioceptive deficits	Bildfell *et al.* 1995 Jolly *et al.* 1994 Nakayama *et al.* 1993 Smith *et al.* 1996
Undefined	Unknown	Abyssinian cats	Ataxia, dysmetria, incoordination, muscle tremors, seizures	Bland van den Berg *et al.* 1977 Lange *et al.* 1977

Key: y: year(s), m: month(s), w: week(s)

* bracket indicates age of onset or age when presented for examination, and different forms of lysosomal storage disease

1.6.1.2 Abiotrophies

As mentioned in Section 1.4.3, abiotrophy means lack of (a-), vital substance necessary for (-bio-), nutritional life of that cell (-trophy). Therefore, it refers to the pathological process of premature neuronal degeneration caused by intrinsic abnormality in the structure that alters the metabolic activity and leads to cell degeneration and death (de Lahunta 1980 a). The underlying cellular defect in most abiotrophies is inherited. In the broadest sense, any inherited degenerative diseases of the nervous system can be termed abiotrophy, which include LSD and other cerebellar degenerative diseases. However, when the underlying cause of the abiotrophy is determined, this should be used in naming the disease (de Lahunta 1990). In this section, abiotrophy refers to degenerative diseases other than LSD. According to de Lahunta (1990), abiotrophies can be divided into four main groups based on the nature of the pathological process: (1) motor neurone degenerative diseases; (2) multisystem degenerations; (3) cerebellar degenerations; and, (4) miscellaneous degenerations. This section will only focus on those diseases relevant to this study (i.e. present with cerebellar dysfunction). In general, the clinical signs progress with time and there is no treatment for this group of disorder.

1.6.1.2.1 Cerebellar abiotrophies

One of the most common abiotrophies in domestic animals is that affecting the cerebellar cortex (de Lahunta 1990). The Purkinje cells are apparently excessively susceptible to intrinsic disturbances of their metabolic apparatus, thus, they are primarily affected. Secondary depletion of the granule neurones usually results due to loss of synaptic relationship with the Purkinje neurones. Furthermore, transsynaptic retrograde degeneration is not usually observed in other neuronal groups that project to the cerebellar cortex such as the olivary and pontine neurones (de Lahunta 1990). The onset of progressive cerebellar ataxia most commonly occurs in the first few weeks of months, however, some animals may show signs at birth or late in life. A neonatal cerebellar abiotrophy has been reported in Beagles (Yasuba *et al.* 1988) and Samoyed (de Lahunta 1983), in which cerebellar signs were noticed at birth. Postnatal cerebellar abiotrophy is more common and has been reported in many breeds. In Rough-coated Collies (Hartley *et al.* 1978) and Gordon Setters (de Lahunta *et al.* 1980, Steinberg *et al.* 1981, Troncoso *et al.* 1985), the disease is inherited as an autosomal recessive trait. Breeds affected with unidentified pattern of inheritance include Airedales (Cordy & Snelbaker 1952), Australian Kelpies (Thomas & Robertson 1989), Border Collies (Gill & Hewland 1980), and Labrador Retriever (Perille *et al.* 1991). Other breeds reported with cerebellar abiotrophy include Akitas, Bernese Mountain dog, Bull Terrier, Cairn Terrier, Clumber Spaniel, Cocker

Spaniel, English Springer Spaniel, Finnish Harrier, Fox Terrier, German Shepherd dog, Golden Retriever, Great Dane, Miniature Poodle (de Lahunta 1983, 1990, March 1996) and mongrel dogs (Nesbit & Ueckermann 1981).

Cerebellar abiotrophy can be presented with quadriplegia and amblyopia which has been recognised in the Irish Setters (Palmer *et al.* 1973, Sakai *et al.* 1994). Chieffo *et al.* (1994) described a syndrome of cerebellar Purkinje cell degeneration and coat colour dilution in a family of Rhodesian Ridgeback dogs. Cerebellar abiotrophy has been diagnosed in the Bernese Mountain Dogs with coexistent hepatocellular abiotrophy (Carmichael *et al.* 1996). Studies have shown an autosomal recessive pattern of inheritance. Although described in many breeds of dogs, cerebellar abiotrophy appeared to be extremely rare in cats, only a few reports in the literature (Taniyama *et al.* 1994, Summers *et al.* 1995, Inada *et al.* 1996, Aye *et al.* 1998). Only the study of Inada *et al.* (1996) showed an autosomal recessive mode of inheritance in the affected cats by experimental breeding.

Onset of cerebellar signs usually occurs early in life, although late-onset cerebellar abiotrophy at 4 years of age has been described in a Schnauzer-Beagle crossbred dog (Chrisman *et al.* 1983) and in Brittany Spaniel dogs between 7 to 13 years of age (LeCouteur *et al.* 1988). In the majority of cerebellar abiotrophies, the predominant microscopic lesion involves loss of Purkinje cells and, secondary depletion of granule cell layer and molecular layer. Tatalick *et al.* (1993) reported an unusual case of cerebellar abiotrophy in a Brittany dog characterised by a marked paucity of granule neurones, a decreased width of molecular and granular layers, and normal numbers of Purkinje cells.

1.6.1.2.2 Multisystem degenerations

This can be further divided into diseases affecting neurones, processes (axons and myelin of neuronal processes), myelin, neuroaxonal dystrophy and neurofilamentous disease (de Lahunta 1990).

Multisystem neuronal abiotrophies

Neuronal cell bodies are primarily affected in this group of disease. Cerebellar and extrapyramidal nuclear abiotrophy has been described in Kerry Blue Terriers (Darke & Kelly 1976, de Lahunta & Averill 1976, Deforest *et al.* 1978, Montgomery & Storts 1983). Neuronal loss in multiple brain regions has been reported in Miniature Poodles (Cummings & de Lahunta 1988), Red-haired Cocker Spaniels (Jaggy & Vandevelde 1988), Swedish Lapland dog (Sandefeldt *et al.* 1973), and multisystemic chromatolytic neuronal degeneration in Cairn

Terriers (Cummings *et al.* 1988, 1991, Palmer & Blakemore 1988, 1989, Hitt *et al.* 1993). Higgins *et al.* (1998) described a late-onset (7-14 years) progressive spinocerebellar degeneration in Brittany Spaniel dogs, with predominantly diffuse Purkinje cell loss, neurofilament accumulation in degenerating cells, in addition to some neuronal degeneration in the brain stem and spinal cord. Affected animals showed cerebellar signs concomitant with other CNS signs. Olivopontocerebellar atrophy has been described in an adult cat (Schut 1946) with chronic degenerative changes in the cerebellar cortex, the bulbar and pontine nuclei associated with the cerebellum.

Multisystem process abiotrophies

This group of multisystem degenerations predominates as focal or diffuse lesions involving the axons and myelin of neuronal processes (de Lahunta 1990). A cerebellar ataxia primarily associated with a myelopathy has been described in Smooth Fox Terriers in Sweden (Björck *et al.* 1957, 1962) and in Jack Russell Terriers in Great Britain (Hartley & Palmer 1973). At a rapid pace, the gait has been described as bounding or dancing in quality. The signs predominantly resemble a cerebellar disorder, however, no lesions have been found in the cerebellum. The major microscopic abnormality is extensive bilateral degeneration of the dorsal part of the lateral funiculus (spinocerebellar tracts) and at the ventromedial sulcus of the ventral funiculus (de Lahunta 1990, Summers *et al.* 1995). Carmichael *et al.* (1983) reported a cerebellar ataxia with hydrocephalus in a family of Bull Mastiff dogs. Microscopic changes include intramyelinic vacuoles which create a spongiform change in all the cerebellar nuclei and other nuclei, with gliosis and spheroids. The following diseases are not described here because they are major degenerative myelopathies with no or minor involvement of the cerebellum. Clinically, animals show a progressive pelvic limb ataxia. They include chronic degenerative radiculomyelopathy (CDRM) in German Shepherd dogs (Averill 1973, Griffiths & Duncan 1975, Braund & Vandevelde 1978), Siberian Huskies (Bichsel & Vandevelde 1983), a miniature poodle (Matthews & de Lahunta 1985), progressive ataxia in a Pyrenean mountain puppy (Wright & Brownlie 1985), and hound ataxia in Harrier Hounds, Beagle Hounds, and Foxhounds (Palmer & Medd 1981, Palmer *et al.* 1984, Sheahan *et al.* 1991).

Multisystem-myelin

This type of abiotrophy predominantly affect central myelin with axonal sparing. Leukoencephalomyelopathy in Rottweilers has been described (Gamble & Chrisman 1984, Slocombe *et al.* 1989, Chrisman 1992). The dogs showed ataxia of pelvic limbs and hypermetria of thoracic limbs. Demyelination with reactive astrocytosis occurred in the central

part of the lateral funiculus, dorsal funiculi, medullary pyramids and cerebellar medulla. A spongy degeneration of the white matter in the CNS in two Labrador Retriever littermates has been described (Zachary & O'Brien 1985, O'Brien & Zachary 1985) which were presented with progressive cerebellar dysfunction. Microscopically, the vacuolisation was most prominent in the cerebellar peduncles, deep cerebellar white matter and cerebral white matter. Ultrastructurally, the vacuolisation (spongy degeneration) was caused by separation of myelin lamellae. Other breeds affected include Australian Silky Terriers (Richards & Kakulas 1978), Samoyeds (Mason *et al.* 1979) which present with congenital generalised tremor. Spongy degeneration has been reported in Egyptian Manu kittens (Kelly & Gaskell 1976) in which the principal neurological signs were ataxia and dysmetria. Other degenerative myelin diseases not presenting with cerebellar signs are described elsewhere (de Lahunta 1990).

Multisystem neuroaxonal dystrophy

Neuroaxonal dystrophy is a morphological abnormality of the axons in central and peripheral nervous systems, manifested by axonal swellings called spheroids (Lowe *et al.* 1997). It is believed that degeneration starts in the distal axon and progresses proximally, resulting in eventual death of the neuronal cell body. Neuroaxonal dystrophy has been described in Border Collies (Clark *et al.* 1982), Chihuahuas (Blakemore & Palmer 1985), a Jack Russell Terrier (Sacre *et al.* 1993), Papillon pups (Franklin *et al.* 1995), Rottweilers (Chrisman *et al.* 1984, Evans *et al.* 1988, Chrisman 1992, Boersma *et al.* 1995), domestic short-haired cats (Woodard *et al.* 1974, Carmichael *et al.* 1993), and Siamese cats (Rodriguez *et al.* 1996). Clinical signs were consistent with a progressive cerebellar disorder in the Border Collies and Chihuahuas, while other CNS signs were also present in other breeds mentioned above. Pathological findings were characterised by numerous axonal spheroids in the cerebellum and other parts of the CNS. In the Border Collies, the Purkinje cells appeared normal, while in the Rottweilers, Siamese and domestic short-haired cats, there was marked loss of Purkinje cells in the cerebellum. A giant axonal neuropathy has been reported in German Shepherd dogs in which the pathology was characterised by axonal swellings in the CNS and PNS (Duncan & Griffiths 1977, 1981, Griffiths & Duncan 1979). Griffiths *et al.* (1980) reported a diffuse axonopathy in young Boxers. Central axonopathy has been described in Labrador Retrievers (de Lahunta *et al.* 1994) and Scottish Terriers (Van Ham *et al.* 1994) which reflected a cerebellar dysfunction. Moreau *et al.* (1991) reported a peripheral and central distal axonopathy in Birman cats.

Miscellaneous

A bilaterally symmetric spongy degeneration of the neuraxis with predominant involvement of the grey matter has been described in two crossbred Malinosis Shepherds which showed generalised tremor and cerebellar dysfunction (Cachin & Vandevelde 1991). The folial cerebellar white matter was markedly vacuolated compared to the relatively normal central cerebellar and cerebral white matter. In the spongy degenerations described above, the white matter was either more severely or exclusively affected. Cachin and Vandevelde (1991) proposed that this appeared to be a distinct syndrome.

A new neurological disorder has been described in young Rottweiler dogs with progressive signs of cerebellar ataxia, spinal ataxia, and tetraparesis/paralysis (Mandigers *et al.* 1995, Kortz *et al.* 1997, van den Ingh *et al.* 1998). The principal microscopic lesion was an intracytoplasmic neuronal vacuolation in the cerebellum, brain stem and spinal cord. The aetiology was not determined.

1.6.2 Angiopathic cerebellar diseases (vascular)

Ischaemia is the reduction of blood flow to an organ which compromises its normal function. During ischaemia, hypoxia and hypoglycemia occur. It is well known that the brain has the least tolerance of all organs to these insults because the brain has the highest energy demand. The neurones and oligodendrocytes are the most vulnerable cells of the neuroectodermal cells and glial cells, respectively. Severe ischaemia in the cerebellum and other parts of the CNS can produce necrosis of neurones and glial elements, resulting in an area of dead tissue described as an infarct (Summers *et al.* 1995). Cerebellar infarction caused by arterial thrombosis has been reported in a dog (Bagley *et al.* 1988), resulting in lateralised cerebellar signs which improved somewhat with time. The infarct caused haemorrhage and malacia of the rostral and middle parts of the left cerebellum supplied by the rostral cerebellar artery. The cause of the thrombus formation in this dog remains unknown. Arterial and venous thrombosis in the dog and cat are thought to be secondary to embolism (cited in Bagley *et al.* 1988). Aberrant migration of parasites, such as, *Dirofilaria immitis*, may result in cerebral infarction. Thrombotic occlusion, resulting in brain haemorrhage, is postulated (cited in Bagley *et al.* 1988) to be related to arterial fibrotic degeneration and artherosclerosis.

Vascular thrombosis in the brain is very uncommon in animals compared to humans. Treatment is mainly symptomatic and supportive, and partial recovery of function is possible.

1.6.3 Anomalous cerebellar conditions

1.6.3.1 Malformation

Occasionally, kittens and puppies are born with a malformed cerebellum that varies in degree from agenesis (Kay & Budzilovich 1970, Harari *et al.* 1983) to hypoplasia, which may be limited to the vermis — Dandy-Walker syndrome (Kornegay 1986 a, Schmid *et al.* 1992, Regnier *et al.* 1993) or may cause diffuse hypoplasia of the cerebellum. In dogs, cerebellar hypoplasia is proposed to be inherited because no infectious causes have been defined (Kornegay 1990 a). Grossly evident forms of uniform cerebellar hypoplasia have been reported in Chow Chows (Knecht *et al.* 1979), Irish Setters, and Wire Haired Fox Terriers (de Lahunta 1980 b), with concomitant lissencephaly present in the latter two breeds. Microscopic examination suggests that these lesions are not the result of inflammation. However, in two other Siberian Husky puppies the presence of inflammatory lesions in the cerebral cortex and brain stem supported the hypothesis of an in utero viral infection causing cerebellar agenesis (Harari *et al.* 1983). Cerebellar hypoplasia characterised by severe depletion of granule cells and almost intact Purkinje cell and molecular layers has been reported in a male 19-month old Beagle dog (Tago *et al.* 1993). However, this is not a typical microscopic feature for cerebellar hypoplasia in which there is reduction of both Purkinje cells and granule cells.

Dandy-Walker syndrome (DWS) of humans has also been reported in dogs (Dow 1940, Oliver & Geary 1965, Pass *et al.* 1981, Schmid *et al.* 1992) and a kitten (Regnier *et al.* 1993). The triad of DWS includes cerebellar vermian hypoplasia, a cyst in the caudal fossa and hydrocephalus. The pathogenesis is not known but it is believed that there is over-distension of the embryonic fourth ventricle *in utero*, due to abnormal impermeability of the primitive caudal medullary velum to CSF, thus interfering with the formation of the cerebellar vermis. Other theories include persistence of the embryonic rostral part of the velum of the fourth ventricle; developmental arrest of the rhombic lips; and impairment of the neuroblast migration through the velum and to nuclear groups of the brain stem (cited in Regnier *et al.* 1993). Although a genetic pattern has not been defined for dogs with cerebellar hypoplasia, many cases probably are inherited. Affected dogs show early onset non-progressive cerebellar signs, sometimes with involvement of the cerebrum due to hydrocephalus, and signs of vestibular dysfunction subsequent to flocculonodular lobe involvement (Schmid *et al.* 1992). Microscopically, the remaining areas of the cerebellar cortex are relatively normal except for focal or scattered evidence of Purkinje cell central chromatolysis and simple atrophy. Retrograde transsynaptic neuronal degeneration may occur in the brain stem nuclei (Kornegay 1986 a).

Recently, an inherited malformation of the CNS of St. Bernard dogs has been described (Franklin *et al.* 1997). Dysplasia of the cerebellar cortex was characterised by loss of normal laminar cytoarchitecture of the cerebellar cortex. Hydrocephalus, pallor and cavitation of the sub-cortical white matter of both the cerebrum and cerebellum were present.

CT and MRI or cisternography, especially in combination with linear tomography can be used as diagnostic aids in evaluation of gross anatomical lesions in the caudal fossa (Schmid *et al.* 1992).

There is no specific treatment for this condition. Anticonvulsants may be indicated if seizures occur subsequent to concomitant hydrocephalus or lissencephaly (Kornegay 1989).

1.6.3.2 Dysmyelinogenesis & hypomyelinogenesis

Dysmyelinogenesis and hypomyelinogenesis are developmental abnormalities, referring to abnormal myelination and reduction in CNS myelin, respectively (Kornegay 1986 b). Microscopically, dysmyelination is characterised by non-myelinated axons and occasional thinly myelinated axons usually ensheathed by abnormal myelin; while hypomyelination is featured by a reduction in CNS myelin, thinly myelinated axons with predominantly normal myelin (Jackson & Duncan 1989). The primary clinical sign is a congenital tremor that affects the entire body, worsens with excitement and subsides with rest. Other signs of cerebellar disturbances such as ataxia, dysmetria and involuntary limb movement may accompany this diffuse myelin deficiency. The syndrome has been described in several breeds of dogs, including Chow Chows (Vandevelde *et al.* 1978, 1981), Springer Spaniels (Griffiths *et al.* 1981), crossbred Lurchers (Mayhew *et al.* 1984), Samoyeds (Cummings *et al.* 1986), Weimaraners (Kornegay *et al.* 1987), Bernese Mountain dogs (Palmer *et al.* 1987), a Dalmatian (Greene *et al.* 1977), and Siamese kittens (Stoffregen *et al.* 1993). Signs in Chow Chows, Weimaraners and the Lurchers usually resolve and disappear by one to two year of age. The diagnosis is made based on the typical clinical signs and their reversible nature in some dogs, which distinguish from the other cerebellar diseases such as LSD or abiotrophies which progress and other cerebellar malformations which remain static (Kornegay 1986 b). Microscopic hallmarks include hypomyelination and dysmyelination without demyelination (Duncan 1987). The cerebellar white matter or the spinocerebellar tracts are involved. Viral infections, genetic defects, intoxications, or idiopathic factors can produce hypomyelination, however, apart from the shaking Springer Spaniel pup in which a genetic basis has been shown, the cause of hypomyelination in other cases could not be determined (Duncan 1987).

1.6.4 Metabolic disorders - Intermediary metabolism disorders

These are inborn disorders in which mutations in enzymes result in deranged metabolism of specific cellular constituents such as amino acids or carbohydrates. In some cases, the disorder affects enzymes within a specific organelle, such as a peroxisome or a mitochondrion (Summers *et al.* 1995). This group of diseases is rarely reported in dogs and cats.

Sudden onset of cerebellar-vestibular signs were observed in 6-8 months old Alaskan Husky dogs by Summer *et al.* (1995) with lesions similar to Leigh's disease or subacute narcotising encephalomyelopathy in humans. This mitochondrial-based disorder consists of an inherited enzyme deficiency that interferes with the ability to metabolise thiamine for its use as a co-enzyme. The disease is progressive and clinical signs reflected a diffuse brain disturbance. The only other report of a similar disease has been described in kittens that showed a fine generalised tremor by 1 month with progressive cerebellar signs, and terminated with visual loss and seizures by 3 months of age (cited in Summers *et al.* 1995). Brain stem and spinal cord lesions were similar to those described in Leigh's disease.

Brenner *et al.* (1997) reported a progressive encephalomyelopathy of insidious onset affecting a 16-month-old female English Springer Spaniel dog. Clinical signs suggested a diffuse or a bilateral and symmetrical lesion with a significant cerebellomedullary component. The neuropathological findings including Purkinje cell loss, astrogliosis and spongiosis, abnormal intraneuronal mitochondrial morphology (megamitochondria) resemble the mitochondrial encephalomyopathies of man.

1.6.5 Neoplasms in the cerebellum

Neoplasms in the cerebellum can be primary, arising from the cells normally found within the cerebellum and the meninges, or secondary, arising from haematogenous metastasis or local invasion from adjacent non-neural tissues. Cerebellar tumours are less common than neoplasms arising in the cerebrum and the brain stem (Kornegay 1990 b).

Non-invasive advanced imaging techniques such as CT and MRI are commonly used to detect primary intracranial tumours in dogs and cats. The CT and MRI characteristics of the canine brain tumours have been described extensively in the literature. Differentiation of different types of tumours is possible based on different intensity patterns (Fike *et al.* 1981, LeCouteur *et al.* 1981, Turrel *et al.* 1986, Kornegay 1990 a, Thomson *et al.* 1993, Shores 1993, Thomas *et al.* 1996). CT-guided stereotactic brain biopsy or intraoperative ultrasound-guided brain biopsy can provided a diagnosis (See Section 1.3.2.3).

Tumours within the caudal fossa tend to have an unfavourable prognosis, as compared to rostral fossa tumours. Due to the critical nature of the neural structures within the caudal fossa, the proximity of these structures to each other and the relatively poor surgical exposure afforded, these tumours are difficult to remove surgically (Adamo & Clinkscales 1991). Long-term corticosteroid therapy may result in transient improvement of the clinical signs. Radiation therapy may be effective, while chemotherapy is of limited efficacy due to the relatively impenetrable blood-brain barrier.

Paradoxical vestibular syndrome (See Section 1.3.1) due to cerebellar neoplasia has been reported in dogs (Palmer *et al.* 1974, LeCouteur *et al.* 1981, Chénier *et al.* 1983, Skerritt & Whitbread 1985, Panciera *et al.* 1987, Adamo & Clinkscales 1991, Muñana 1991, Schulman *et al.* 1992), and in cats (Smith & Honhold 1988, Quesnel & Parent 1995).

1.6.5.1 Medulloblastoma

Medulloblastomas or cerebellar neuroblastomas are rare, undifferentiated tumours which arise from the external germinal cell layer of the cerebellum *in utero*, and selectively involve the cerebellum. Medulloblastomas tend to occur in juvenile animals (Johnson 1990), grow relatively rapidly and can metastasise to the meninges via the CSF (cited in Kornegay 1990 b). This tumour has been reported in dogs and cats, and appears to be even more rare in cats than dogs (Kornegay 1990 b). The tumour can be laterally situated or on the midline of the cerebellum.

1.6.5.2 Meningioma

Meningiomas are one of the most common primary intracranial neoplasm in dogs, and are the most frequently occurring intracranial neoplasms in cats especially in middle aged or older animals (Luginbuhl 1961, Zaki & Hurvitz 1976, Braund & Ribas 1986, Moore *et al.* 1996). The majority are located over the convexity of the cerebral hemispheres. Involvement of the caudal fossa and cerebellum by meningiomas has been reported in dogs and cats, although less commonly (Nafe 1979, LeCouteur *et al.* 1981, Patnaik *et al.* 1986, Kornegay 1990 b, 1991 b, Adamo & Clinkscales 1991, Muñana 1991, Schulman *et al.* 1992, Quesnel & Parent 1995). In the review of 50 cases of canine CNS meningiomas by Ribas *et al.* (1991), 6 meningiomas (12%) arose in the cerebellum. Multiple malignant meningiomas were diagnosed in a young cat presented with diffuse cerebellar signs induced by lymphoma chemotherapy (Lobetti *et al.* 1997).

Meningiomas are believed to derive from the arachnoid cap cells or arachnoid granulations especially where arachnoid cells are associated with the venous sinuses of the dura (Summers *et al.* 1995). Hyperostosis of the calvarium may occur (Moore *et al.* 1996) and be visible on skull radiographs. Histological patterns and ultrastructural features of canine meningiomas have been described in detail by Summers *et al.* (1995). Immunohistochemically, canine meningiomas commonly express vimentin intermediate filaments (Summers *et al.* 1995).

1.6.5.3 Glioma

1.6.5.3.1 Astrocytoma

Astrocytoma is a tumour arising from astrocytes. It is the most common primary canine brain tumour with a predilection for the cerebrum, although it may also occur in the thalamus, hypothalamus, and the brainstem (Johnson 1990). Astrocytomas have also been described in the cerebellum of the dog (Panciera *et al.* 1987, Lenz *et al.* 1991). GFAP is the most specific cell marker for astrocytomas (Johnson 1990).

1.6.5.3.2 Oligodendroglioma

Oligodendrogliomas usually arise from the cerebrum in the dogs and cats. However, an unusual cerebellar oligodendroglioma has been reported in a cat, causing a progressive paradoxical vestibular syndrome (Smith & Honhold 1988).

1.6.5.4 Choroid plexus tumour

Choroid plexus tumour (CPT) is a rare neuroepithelial tumour which arises from the epithelial cells lining the choroid plexus of the lateral, third, and fourth ventricles. These tumours can be classified as choroid plexus papillomas or choroid plexus carcinomas based on their histological appearance and biological behaviour (Moore *et al.* 1996). In dogs, the fourth ventricle appears to be the predilection site (Zaki & Nafe 1980, Moore *et al.* 1996). In one report of choroid plexus papillomas in the dog, seven out of nine tumours occurred in the fourth ventricle (Zaki & Nafe 1980), and in another report of fifteen canine CPTs, 60% occurred in the fourth ventricle (cited in Zaki & Nafe 1980).

CPT of the fourth ventricle may extend through the lateral aperture into the cerebellopontine angle and compress the cranial nerves V, VII, VIII as well as the ventrolateral aspect of the cerebellum and rostral medulla oblongata (Indrieri *et al.* 1980, LeCouteur *et al.* 1981). The tumour may also cause compression and subsequent degeneration of these cranial nerve nuclei within the pons and medulla. Secondary hydrocephalus of the lateral and third ventricles may occur due to occlusion of the fourth ventricle and subsequent interference with normal CSF circulation by the tumour (Indrieri *et al.* 1980). CPT of the fourth ventricle in dogs may cause paradoxical vestibular syndrome (Skerritt & Whitbread 1985, Chénier *et al.* 1983).

Analysis of CSF may identify tumour cells, and elevation of protein concentration. Canine choroid plexus papillomas appear negative immunohistochemically for GFAP in contrast to those in humans (Summers *et al.* 1995).

1.6.5.5 Intracranial epidermoid cyst

Intracranial epidermoid cysts (IEC) are rare, benign tumours that arise from heterotopic epithelium. They are lined by squamous epithelium and contain intraluminal keratinaceous debris. Like CPT, IEC also tend to selectively arise at the cerebellopontine angle or in the fourth ventricle in young animals, and often compress the cerebellum and the rostral medulla oblongata (Kornegay & Gorgacz 1982), resulting in cerebellar-vestibular dysfunction or central vestibular signs. However, no obvious cerebellar signs may be seen if the compression atrophy of the surrounding cerebellar folia is mild, as occurred in a dog with multiloculated IEC (Kawaminami *et al.* 1991). Human IEC are thought to occur due to inclusion of non-neural ectoderm at the time of closure of the neural tube. In one report, five out of six dogs were 2 years of age or younger, which is consistent with the probable congenital origin of the lesion (Kornegay & Gorgacz 1982). Late onset of clinical signs has been reported in aged dogs (Kornegay & Gorgacz 1982, O'Brien *et al.* 1990), probably due to slow enlargement and their

tendency to conform around structures rather than compressing them. Rupture of the cyst can release cholesterol crystals and keratin into the CSF which may elicit a foreign body reaction leading to suppurative meningitis (O'Brien *et al.* 1990).

1.6.5.6 Lymphoma (Lymphosarcoma)

Lymphoma of the CNS may occur as part of the clinically-apparent multicentric form. Systemic lymphomas can affect the CNS by forming extradural compressive masses, diffusely infiltrating the leptomeninges to resemble meningitis, or forming intraparenchymal masses (Johnson 1990). Primary brain malignant lymphoma is extremely uncommon and primary intracerebellar lymphosarcoma is even rarer. Diffuse meningeal involvement or extradural masses may contribute to cerebellar signs. A solitary extranodal lymphoma confined to the cerebellum causing generalised cerebellar signs in a young dog, has been reported (Lefbom & Parker 1995).

1.6.5.7 Miscellaneous neoplasms

Primary tumours of the adjacent tissue (osteo-, lipo-, fibro-, hemangio-, and chondrosarcoma, adenocarcinoma, myeloma) or metastatic tumours may affect the cerebellum, but they are very uncommon.

1.6.6 Nutritional disease affecting the cerebellum - thiamine deficiency

Thiamine deficiency in cats and dogs is caused by feeding on diets deficient in thiamine or high in raw fish which contains a thiaminase. Thiamine deficiency produces characteristic clinical signs and pathology in cats (Everett 1944, Jubb *et al.* 1956, Loew *et al.* 1970) and dogs (Read *et al.* 1977, Read & Harrington 1981), either in experimentally-induced or naturally-occurring cases. According to Everett (1944), the clinical syndrome can be divided into 3 stages. In the induction stage, there is a progressive decline in food consumption, followed by complete anorexia, weight loss, occasional vomiting and excessive salivation. The critical phase is indicated by development of acute nervous signs, including ataxia and hypermetria which are suggestive of cerebellar dysfunction. Ventroflexion of the head while the animal is being suspended by hind limbs, mydriasis, slow and incomplete pupillary light reflexes are consistent findings in affected cats. Convulsions, spastic clonus and hyperaestheisa to touch and noise are also features of the critical stage. If untreated at this stage, the animal will progress rapidly to the terminal irreversible stage of semi-coma, continual crying, opisthotonus and maintained extensor tone (Jubb *et al.* 1956) followed by death.

A diagnosis of thiamine deficiency can be made from low blood thiamine concentration. Thiamine has an important role as a coenzyme in carbohydrate metabolism, both in the tricarboxylic acid and the pentose pathways. In thiamine deficiency, inhibition of carbohydrate metabolism results in elevated levels of blood lactate and pyruvate, and lowered transketolase activity (cited in Summers *et al.* 1995). Pathologically, the disease is characterised by bilateral symmetrical haemorrhages in the midbrain periventricular grey matter. Microscopically, oedema and neuronal necrosis are present in the brainstem nuclei. Similar lesions also occur in the cerebellum and cerebral cortex in the dogs. Read *et al.* (1977) described the lesions in the cerebellar vermis which included spongy change and parenchymal necrosis of the molecular, Purkinje cell and granule cell layers.

Rapid progressive improvement to thiamine supplementation (multiple B vitamin preparation in the form of injections or tablets) may be seen within days if the animal is treated during or before the critical stage. Dosage recommended is 75 mg thiamine given twice daily (Loew *et al.* 1970).

1.6.7 Cerebellar diseases caused by infectious diseases

Infection in dogs and cats can affect primarily the cerebellum, though most animals will have lesions elsewhere in the CNS, as well as systemic signs. Thus cerebellar signs may be subtle or prominent depending on the case. However, on necropsy, the cerebellum is usually involved in the disease process. In general, most infectious cerebellar diseases are progressive, without treatment and, in many cases, regardless of treatment. The two exceptions are cerebellar hypoplasia caused by feline panleukopaenia virus and cerebellar dysplasia caused by canine herpesvirus.

1.6.7.1 Viral diseases

1.6.7.1.1 Feline Panleukopaenia Virus (FPV)

Cerebellar hypoplasia may occur in kittens born to queens infected *in utero*, or perinatally by FPV. The virus has cytopathic effects on the external germinal cell layer of the cerebellum. The active proliferating and differentiating process of the granule cell is interrupted and destroyed, leading to hypoplasia of the granule cell layer. The molecular layer is often thin which may be due to the relative absence of granule cell axons in this layer. Postmitotic Purkinje cells also may degenerate, presumably because of a separate direct cytopathic effect of the virus (Csiza *et al.* 1972). Margolis (1971) has proposed that the virus has a particular affinity or tropism for Purkinje cells, possibly mediated by antigen-antibody interactions. Severe destruction may result in a few rudimentary folia remaining over the cerebellar medulla. The cerebellar hemispheres and dorsal portion of the vermis are preferentially affected. Rarely, intrauterine FPV infection also has been associated with hydrocephalus (Kilham & Margolis 1966, Csiza *et al.* 1971 a) and hydranencephaly in kittens (Greene *et al.* 1982), either alone or in conjunction with cerebellar hypoplasia. Chronic inflammatory cells in the meninges, lymphocytic perivascular cuffings, glial nodules and myelin degeneration are other abnormal histopathological findings (Csiza *et al.* 1972). Although postnatal infection with FPV may cause systemic disease, it rarely causes inflammation of the CNS and resulting clinical signs. Nevertheless, it is possible that the adult cat suffers simultaneously from both gastrointestinal and acute neurological syndromes of FPV, if it is severely compromised by conditions such as stress and surgery-related immunodeficiency (Foley 1993).

Clinical findings include symmetrical, non-progressive, generalised cerebellar signs when the kitten is ambulatory at around 3-4 weeks of age. There is no apparent breed or sex predilection. More commonly, one kitten rather than the entire litter, is affected. Spasticity with markedly

inco-ordinated dysmetric limb movements, truncal swaying, and loss of balance (i.e. a tendency to fall to either side, backwards, or forwards) are usually observed. These kittens often have a broad-based stance and may sit on their rumps with their thoracic limbs extended, which has been referred to as 'tripod sitting posture' (Carpenter & Harter 1956). A fine head tremor is occasionally observed, but abnormal nystagmus is unusual (de Lahunta 1983). Bilateral absence of menace response is common. Kittens with hydrocephalus or hydranencephaly may have additional signs of forebrain disease. In kittens with sole cerebellar involvement, slight improvement may be noted because of accommodation through other senses such as vision and conscious proprioception (Kornegay 1991 b). The cerebellar signs are life-long.

A tentative diagnosis can be made from the history and clinical observation for several months to confirm static signs of strict cerebellar dysfunction. However, achieving a definitive antemortem diagnosis of FPV infection may be difficult. Serum antibodies in kittens less than 3 months of age can be maternally-derived and hence non-diagnostic (Csiza *et al.* 1972). Csiza *et al.* (1971 b) have shown that serum-neutralising antibody titres remain constant for at least 10 months in naturally-occurring FPV infected cats, with prolonged persistence of virus in the body. MRI may be helpful in identifying hypoplastic or otherwise malformed cerebella in kittens (Kornegay 1989, Thomson *et al.* 1993). Isolation of the FPV from the brain or other organs provides the most definitive diagnosis, however, characteristic lesions can only be fully defined with necropsy. The severity of cerebellar hypoplasia varies, some affected cats may have relatively normal-sized cerebellum, thus histopathological examination is required to look for paucity of granule and Purkinje cells in the cerebellum.

Although there is no specific treatment for cerebellar hypoplasia, some affected animals can be acceptable pets if kept in a protected environment, especially those with only mild signs which are not debilitating (Shell 1996).

1.6.7.1.2 Canine Herpesvirus (CHV)

CHV infection in puppies during the first 2 weeks of life is a peracute, fatal, systemic disease. Percy *et al.* (1971) described segmental cerebellar and retinal dysplasia in a 31-day-old Malamute puppy with naturally-occurring CHV infection, suggesting that CHV may impair the normal differentiation of the cerebellar or retinal tissues. Occasionally, puppies surviving an infection with CHV during the first week of life, will develop a residual cerebellar ataxia, which is secondary to the destructive effect of the virus on various components of the cerebellum. The cerebellar signs are non-progressive and life-long.

1.6.7.1.3 Canine Distemper Virus (CDV)

CDV is a paramyxovirus which is the most common known aetiology of inflammatory brain disease in dogs. CDV typically affects young, unvaccinated dogs, however, fully vaccinated mature dogs can also be affected. Infection in immature dogs usually results in acute polioencephalomyelopathy (PEM) and high mortality rate while mature dogs principally develop a chronic leukoencephalomyelopathy (LEM) with a lower mortality (cited in Thomas *et al.* 1993 b). Gait deficits and vestibular dysfunction are common neurological signs in dogs with LEM (Thomas *et al.* 1993 b). Retinochoroiditis is present on fundoscopic examination in many affected dogs. Analysis of CSF typically demonstrates a mild lymphocytic pleiocytosis characteristic of viral infection. Paired serum and CSF antibody titres demonstrating a CSF antibody titre greater than that of serum is indicative of local immunoglobulin production associated with infection (Muñana 1996). Demonstration of a rising neutralising antibody titre in the serum and CSF is also definitive (Higgins *et al.* 1989). Concurrent measurement of antibody titres to parvovirus or adenovirus in CSF and serum ensures that CSF-CDV titres are not a consequence of a damaged blood brain barrier. The cerebellum is commonly affected in dogs with CDV (de Lahunta 1983), resulting in demyelination and, less commonly, neuronal necrosis. In LEM, histopathological examination identifies demyelination, white matter necrosis and abundant perivascular inflammatory infiltrates in the cerebellum, brain stem and spinal cord (Muñana 1996). The foci of demyelination are noted in both cerebellar medullary and folial white matter.

In general, the neurological form of CDV carries a very poor prognosis. No specific treatment is known and is, thus, mainly supportive and symptomatic. Anticonvulsants are indicated in dogs with seizures (Muñana 1996).

1.6.7.1.4 Feline Infectious Peritonitis Virus (FIPV)

FIP is a coronavirus-induced systemic infection of cats. Neurological manifestations of FIP are seen predominantly in cats with the non-effusive or dry form (Kornegay 1978, Kline *et al.* 1994), although occasionally the effusive form is incriminated (Hopkins 1992). The pathogenesis of FIP involves immunopathological mechanisms. In non-effusive disease, cats mount a partial cell-mediated immune response combined with a strong humoral response to FIP. This response limits viral replication but fails to destroy the virus. Thus immune complexes are formed and deposited around vessels, resulting in vasculitis. The vascular changes incite pyogranulomatous inflammatory response, with multiple pus-containing granulomatous lesions surrounding virus-laden macrophages (Grahn 1991, Hoskins 1991,

McReynolds & Macy 1997). Up to 10-25% of cats with FIP eventually develop multifocal, progressive neurologic signs (McReynolds & Macy 1997). CNS signs are variable (Kornegay 1978, Kline 1994) and although diffuse or multifocal signs are typical of FIP, pure localised signs may be seen. Signs referable to cerebellomedullary involvement, including spastic paresis, ataxia, nystagmus and balance loss, are the most common CNS signs. FIP meningoencephalitis is the most common inflammatory disorder of the feline neuraxis (Summers *et al.* 1995). Kline *et al.* (1994) reported 24 cats with histopathologically-diagnosed FIP involving the nervous system in which the neurological lesions were localised to the cerebellum in 10 cats. Cerebellar signs included progressive ataxia, intention tremor (head, trunk, or both), hypermetria, absence of menace responses, and one cat also demonstrated a decerebellate posture.

Diagnosis of FIP has been described extensively in literature (Shelly *et al.* 1987, Grahn 1991, Hoskins 1991, Weiss 1991, Sparkes *et al.* 1994, Muñana 1996, McReynolds & Macy 1997). The neurological form of FIP tends to have an insidious onset with no specific clinical course. Concurrent systemic signs such as anorexia, weight loss, pyrexia are usually present. Ocular lesions often associated with FIP are anterior uveitis, corneal oedema, keratic precipitates, aqueous flare, fibrinohaemorrhagic clot formation, miosis, and posterior synechia (Doherty 1971, Quinn 1987, Miller & Johnson 1989). Haematological changes are variable and not specific for FIP. Affected cats may show a progressive non-regenerative normochromic, normocytic anaemia; neutrophilic leukocytosis and lymphopaenia. Serum biochemical abnormalities and urinalysis reflect the organs involved and the extent of disease (McReynolds & Macy 1997). Hyperproteinaemia is detected in 75% of the cases of non-effusive FIP (Pederson 1976) due to hyperglobulinaemia. Serum protein electrophoresis reflects variable increases in α-2 and β globulins, and polyclonal (sometimes monoclonal) gammopathy (Weiss 1991). Serum titre of feline coronavirus (FCoV) may be very high in suspected cases of dry FIP but this is non-specific (Weiss 1991). No single indicator of FIP (e.g. the diagnostic profile, complete blood count, polymerase chain reaction (PCR), or FCoV serology) is sufficiently reliable to confirm an antemortem diagnosis of FIP. However, a combination of these indicators is very suggestive of FIP infection (McReynolds & Macy 1997). The finding of hydrocephalus on CT scan in cats with signs associated with FIP may aid in antemortem diagnosis (Kline *et al.* 1994). CSF analysis is considered the most useful test in establishing an antemortem diagnosis of dry FIP (Muñana 1996). Marked pleiocytosis (mononuclear, mixed mononuclear, or polymorphonuclear) concomitant with a marked increase in protein concentration (often exceeding 2 g/L) are consistent with FIP infection. PCR has been developed for the detection of FCoV in faeces, tissues, and body fluids of infected cats

(Herrewegh *et al.* 1995). FCoV antibody titre and PCR can be performed on CSF to confirm the diagnosis.

Histopathological examination of the CNS reveals a severe pyogranulomatous leptomeningitis, choroiditis, ependymitis, and encephalomyelitis (Summers *et al.* 1995). Similar histological lesions may be seen in cats showing no obvious evidence of neurologic dysfunction (Kornegay 1978). Moreover, hydrocephalus and hydromyelia are common findings. In the report of Kline *et al.* (1994), all cats with FIP had some degree of hydrocephalus on histological examination. The prognosis for cats with neurological FIP is very poor. Conventional therapy with cytotoxic agents and corticosteroid may prolong life. A combination of immunomodulating agents and antiviral drugs together with anti-inflammatory or cytotoxic drugs may be required to achieve a more successful treatment (Weiss 1995). To date, however, there is no known effective treatment.

1.6.7.1.5 Feline Immunodeficiency Virus (FIV)

Neurological disease can occur in FIV infection, though it is not common. FIV is a lentivirus which is neurotropic (Dow *et al.* 1990, Dow *et al.* 1992). About 5% of clinically-ill FIV-infected cats will demonstrate neurological signs (Pedersen *et al.* 1989, 1991), especially in cats with advanced disease (Dow *et al.* 1992). Neurological disease is usually a direct effect of the virus on brain cells, or less commonly a manifestation of some other opportunistic infections such as FIPV and toxoplasmosis (Muñana 1996). Most neurological signs reflect lesion localisation in the cerebral cortex and they are characterised primarily as behavioural disorders. Ataxia, intention tremors, nystagmus and other motor deficits occur less commonly (Hopper *et al.* 1989, Dow *et al.* 1992, Phillips *et al.* 1994). CSF analysis may demonstrate a mild pleiocytosis and protein concentration is usually normal (Muñana 1996). Diagnosis of FIV-associated encephalopathy can be made by detecting antibodies to FIV, and culturing of CSF or brain tissue from several brain regions including the cerebellum (Dow *et al.* 1990).

Histopathological examination of experimentally infected cats revealed a mild, non-supportive meningoencephalitis with glial nodules and mononuclear cell perivascular cuffing in the grey and white matter (Summers *et al.* 1995). No therapy has been proven effective in the management of FIV-associated encephalopathy (Muñana 1996).

1.6.7.2 Protozoal diseases

Protozoal encephalomyelitis can affect the cerebellum in dogs and cats. Clinical signs suggest focal or multifocal disease and may reflect cerebral, brain stem, cerebellar or spinal cord

involvement (Summers *et al.* 1995). CSF analysis may reveal a pleiocytosis of macrophages, neutrophils, lymphocytes or eosinophils and raised protein concentration. Characteristic histopathological findings include non-suppurative meningoencephalomyelitis affecting grey and white matter, mononuclear perivascular cuffing, necrotising inflammation and granuloma formation.

1.6.7.2.1 Toxoplasmosis

Toxoplasma gondii is a coccidian parasite for which the cat is the definitive host and any warm-blooded animal (such as dogs) may act as an intermediate host. Concurrent ocular abnormalities such as anterior uveitis and multifocal chorioretinitis may be present on fundoscopic examination (Miller & Johnson 1989). *T. gondii* has been described in dogs causing ataxia and progressive paraparesis (Nesbit *et al.* 1981, Morales *et al.* 1995) with diffuse lesions in the CNS and other tissues. Although the clinical signs may not reveal cerebellar involvement, microscopic lesions in the cerebellum are usually striking. Histopathologic examination may reveal non-suppurative meningo-encephalitis, degeneration and necrosis of the cerebellar cortex and adjacent white matter, gliosis, perivascular cuffs and infiltration of lymphocytes, plasma cells and macrophages. Diagnosis can be made by immunohistochemical reaction of tachyzoites and tissue cysts with *T. gondii* antibodies (Muñana 1996). Clindamycin hydrochloride 25 mg/kg divided two or three times daily can be used to treat CNS toxoplasmosis. Trimethoprim-sulpha 15 mg/kg orally every 12 hours can also be used. Neurological signs usually improve with treatment but may not resolve completely due to permanent damage caused by the infection (Muñana 1996).

1.6.7.2.2 Neosporosis

Neospora caninum is a canine parasite that may cause polyradiculoneuritis, polymyositis, lower motor neurone deficits of the pelvic limbs, bladder and rectum. In immature dogs particularly, affected dogs are presented with progressive paraparesis and hyperextension of the pelvic limbs (Knowler & Wheeler 1995). Less commonly, cerebellar signs may be the predominant clinical feature. Atrophy of cerebellar folia was reported in a group of six dogs congenitally infected with *N. caninum* (Bjerkas & Presthus 1989). Jackson *et al.* (1995) described neosporosis as the cause of a chronic encephalitis with profound cerebellar atrophy in a 3.5 year-old dog. Progressive cerebellar ataxia since 14 months of age and atrophy of selective muscle groups were the main clinical features. Barber *et al.* (1996) reported neosporosis in an adult dog with a chronic history of ataxia, exaggerated spinal reflexes with mild spasticity, decreased proprioceptive reflexes, intermittent head nodding and other signs.

N. caninum is similar to *T. gondii*, but there are ultrastructural differences such as cyst wall thickness and antigenic dissimilarities, thus allowing identification by immunocytochemistry (Dubey *et al.* 1988, Lindsay & Dubey 1989). Barber *et al.* (1996) reported that parasite density varied markedly in individual cases, and although found most consistently in the cerebrum, parasites were distributed throughout the CNS, both within the grey and white matter and within nerve roots. In addition, clinical signs were not related to the position of the parasites. Tissue cysts containing bradyzoites were found infrequently in all areas of the CNS and eye, but not in other tissues. However, the tissue cysts often provoke little or no host cell response (cited in Barber *et al.* 1996). The clinical signs result from death of host cells following rapid intracellular multiplication of the parasite and the ensuing inflammatory response (Barber *et al.* 1996).

Neosporosis can be diagnosed antemortem by a titre equal or greater than 1:50 in *N. caninum* indirect fluorescent antibody test [IFAT] (Dubey *et al.* 1988, Trees *et al.* 1993), or by demonstration of species-specific antibodies in both serum and tissue sections. Histopathological examination may reveal tachyzoites or tissue cysts, and a diagnosis is confirmed by positive immunohistochemical staining (Dubey *et al.* 1988, Lindsay & Dubey 1989). In general, a multifocal non-suppurative meningoencephalitis is seen characterised by gliosis and perivascular infiltration by mononuclear cells. The cerebellum is commonly involved. A more localised syndrome may be encountered. Morales *et al.* (1995) described a dog with cerebellar malacia caused by protozoal tachyzoites. Although there was a diffuse non-suppurative meningoencephalitis, the most severe lesion was located in the cerebellar cortex and adjacent white matter, consisting of granulomatous, eosinophilic meningo-encephalitis with extensive areas of necrosis, perivascular cuffing, and neovascularisation. Protozoal tachyzoites were found particularly in necrotic areas and in blood vessels walls.

Treatment of neosporosis is similar to that of toxoplasmosis, with the use of clindamycin at 10 to 40 mg/kg orally, divided two or three times daily or trimethoprim/sulphonamide at 15 mg/kg orally two to three times daily and oral pyrimethamine at 1 mg/kg daily for at least 4 weeks. A folic acid supplementation is also recommended (Mayhew *et al.* 1991, cited in Knowler & Wheeler 1995).

1.6.7.2.3 Babesiosis

Babesia canis is a tick-transmitted protozoan organism that parasitises erythrocytes in dogs. Jacobson (1994) described cerebellar signs in 2 dogs infected with *Babesia canis*, including ataxia, intention tremor and variable menace response, and suggested that cerebellar ataxia

should be considered a possible complication of canine babesiosis. Malherbe & Parkin (1951) described a dog with babesiosis which showed hypermetria of the fore limbs. The cerebellar signs resolved following treatment including trimethoprim-sulfamethoxazole, prednisolone, and dimethylsulfoxide (Jacobson 1994).

1.6.7.3 Rickettsial diseases

Ehrlichiosis and Rocky Mountain Spotted Fever (RMSF) are rickettsial diseases which may cause cerebellar signs (Oliver & Lorenz 1993). However, they are not recognised in the United Kingdom.

Ehrlichia canis is an intracellular parasite transmitted to dogs by the brown dog tick *Rhipicephalus sanguineus*. Neurologic signs occur in approximately one third of clinically affected dogs (Greene *et al.* 1985). Clinical signs result from organism-induced vasculitis and the host inflammatory response. CNS signs include seizures, vestibular dysfunction, cerebellar dysfunction and hyperaesthesia which are due to meningitis (Muñana 1996). Concurrent systemic signs are usually present. CSF analysis reveals a mild mononuclear pleiocytosis with elevated protein concentration. Diagnosis can be made by detecting a positive *E. canis* titre in serum or CSF. Histopathologic findings are characterised by meningitis of mononuclear cell type (Summers *et al.* 1995), and perivascular lymphoplasmacytic infiltration of the brain parenchyma. Tetracycline antibiotics are used to treat this disease.

RMSF is caused by *Rickettsia rickettsii*. CSF analysis may reveal a suppurative pleiocytosis with a mild increase in protein level. Diagnosis is based on a single markedly increased serum titre or paired rising titres or by immunofluorescent procedures (Greene *et al.* 1985). Neuropathological examination reveals a necrotising vasculitis with perivascular infiltration of neutrophils and mononuclear cells, and small areas of parenchymal necrosis with neutrophilic invasion (Summers *et al.* 1995). Treatment with tetracycline or related compounds is recommended (Muñana 1996).

1.6.7.4 Fungal diseases

Cryptococcus neoformans is a saprophytic yeast-like fungus which can affect the cerebellum in dogs and cats (de Lahunta 1983). CSF analysis often reveals a neutrophilic pleiocytosis and in some cases, an increase in eosinophils. Diagnosis of CNS cryptococcosis can often be made by cytological evaluation of CSF, detecting the organism in CSF (staining with Indian ink, new methylene blue, Gram's stain), detecting cryptococcal capsular antigen in the serum or CSF, or by culturing the organisms from CSF samples (Muñana 1996). In cats a mild non-suppurative

meningoencephalitis is seen microscopically; in contrast, a more granulomatous inflammatory response is seen in dogs (Summers *et al.* 1995). Treatment of CNS cryptococcosis is still under evaluation.

1.6.7.5 Parasitic diseases

Parasitic migration may occur through the cerebellum and produce signs of cerebellar and/or vestibular dysfunction (de Lahunta 1983). A *Cuterebra* larva has been observed in cats (de Lahunta 1983). The CSF analysis may show a predominance of neutrophils which is probably a response to necrosis (Summers *et al.* 1995). Aberrant migration of *Dirofilaria immitis* in the CNS of the dogs and cats has been encountered. Carlisle *et al.* (1984) and Fukushima *et al.* (1984) reported aberrant dirofilariasis in a dog and cat respectively, in which gross examination demonstrated *D. Immitus* protruding through the cerebellar vermis. Although the affected animals did not show cerebellar signs, microscopically, choriomeningo-encephalitis and granulomatous meningitis were induced by the parasite.

1.6.7.6 Feline Spongiform Encephalopathy (FSE)

FSE is a novel, naturally occurring scrapie-like disease of domestic cats (Pearson *et al.* 1993). The first case of FSE in a domestic cat was identified in April 1990 in the UK by Wyatt *et al.* (1990). More cases have been reported in domestic and non-domestic cats since then (Leggett *et al.* 1990, Pearson *et al.* 1991, Wyatt 1991, Wyatt *et al.* 1991, Synge & Waters 1991, Willoughby *et al.* 1992, Wyatt *et al.* 1993, Bratberg *et al.* 1995).

The aetiology of FSE is not well understood, although the evidence points to a feed source and probable origin from bovine spongiform encephalopathy (BSE) rather than scrapie (Anon 1995). There is no breed or sex predilection. Middle-age to old cats are more likely to be affected, though the youngest cat being reported was only 2 years old (Gruffydd-Jones *et al.* 1991). The clinical signs are insidious in onset, develop slowly over several weeks. Clinical signs reported in cats with FSE are listed in Table 4. Progressive locomotor dysfunction with hind limb ataxia, cerebellar signs especially dysmetria, and behavioural changes (i.e. increased timidity or aggression) are usually the first signs noticed by the owners. More advanced cases progressed to involve forelimb ataxia, often with a rapid, crouching, hypermetric gait (Pearson *et al.* 1993). Other common signs include hyperaesthesia to touch and sound, dilated but responsive pupils, hypersalivation and polyphagia. A tentative diagnosis can be made from the history and a combination of the characteristic clinical features. CSF analysis is not a useful diagnostic test in FSE. The neurological signs usually progress rapidly over several weeks. As

no treatment is available at present, therefore, euthanasia is usually performed on humane grounds.

A definitive diagnosis is based on histopathological examination of the formalin-fixed tissue, demonstration of scrapie-associated fibrils and modified protease-resistant prion protein (PrP) of the fresh frozen brain and spinal cord. PrP is a host-coded membrane glycoprotein which becomes modified to a disease specific isoform PrP^{SC} by infection with the agents causing scrapie, BSE, and related encephalopathies. PrP^{SC} can be detected by immunoblotting and immunocytochemical methods which require antisera that can distinguish protease-resistant PrP from its normal cellular precursor in a range of species (Wells & McGill 1992). Detergent extraction of PrP^{SC}, followed by protease treatment, results in a protease-resistant core protein which may be demonstrated by negative staining on electron microscopy in the form of abnormal fibrils called scrapie-associated fibrils (Pearson *et al.* 1992). The fibrils and modified PrP are diagnostic criteria of the transmissible spongiform encephalopathies, and fibril and PrP studies of FSE have been described in details by Pearson *et al.* (1992). Principal histopathological findings in FSE reveal changes pathognomonic of the transmissible spongiform encephalopathies, including vacuolation of the neuropil and neuronal perikarya throughout the neuroaxis and an astrocytic gliosis (Wyatt *et al.* 1991, 1993). Perivascular cuffing or meningeal infiltration of inflammatory cells have not been observed.

It is possible that screening for scrapie-associated fibrils and modified PrP in lymphoreticular tissues, such as lymph nodes or tonsils, might enable antemortem diagnosis (Gruffydd-Jones *et al.* 1991).

Table 4. Clinical signs reported in cats with FSE

Cerebellar signs	Ataxia Hypermetria Intention tremor
Behaviour changes	Aggression or timidity Hyperaesthesia (tactile or auditory) Altered grooming (ceased, decreased or increased) Teeth grinding/ jaw champing Crouching gait
Miscellaneous	Mydriasis (intermittent) Hypersalivation/drooling Muscle tremors/ fasciculations Hyperreflexia Polydipsia Polyphagia Aberrant urination and defecation Inability to retract claws Impaired vision Head pressing Weight loss

(Gruffydd-Jones *et al.* 1991, Pearson *et al.* 1993, Anon 1996)

1.6.8 Inflammatory cerebellar diseases of unknown aetiological origin

Inflammation of unknown aetiology involving the cerebellum will be discussed in the following. An immunological basis is probably the most likely aetiologies in most circumstances.

1.6.8.1 Granulomatous Meningoencephalomyelitis (GME)

Granulomatous meningoencephalomyelitis (GME) is a sporadic, idiopathic, inflammatory disease of the CNS (Braund *et al.* 1978). The lesion is characterised histologically by disseminated or focal non-caseating granulomas in the CNS, non-suppurative meningitis, marked perivascular histiocytic and lymphoplasmacytic cuffing. The disseminated form has been described previously as inflammatory reticulosis, granulomatous reticulosis, and histiocytic encephalitis; while the local form has been described as neoplastic reticulosis (Braund 1985). An ocular form of GME has also been described. GME is seen in dogs of all ages and breeds. Most cases occur in mature adult dogs, and females seem to be affected more often (Cordy 1979, Braund 1985, Bailey & Higgins 1986 b, Sorjonen 1990), although in the study of Thomas and Eger (1989), male dogs predominated.

Clinical signs reflect the site of lesions in the neuraxis, which are located predominantly in the white matter of the cerebrum, caudal brain stem, cerebellum and cervical spinal cord (Braund 1985). Disseminated GME usually is manifested by acute progressive multifocal neurological signs, though signs may be confined to a part of the CNS, for instance, the caudal fossa (Glastonbury & Frauenfelder 1981). A neutrophilic leukocytosis may be found in the more acute febrile cases. CSF analysis is considered the best indicator of GME (Sorjonen 1990) and may reveal marked pleiocytosis with a predominantly mononuclear cell population and elevation of protein concentration (Braund *et al.* 1978). However, in a retrospective study by Bailey and Higgins (1986 b) a substantial percentage of polymorphonuclear cells has been identified in several cases.

Focal GME may produce clinical signs suggestive of a single, space-occupying lesion which resembles intracranial neoplasia clinically, and CT evaluation may reveal a contrast-enhancing mass lesion (Speciale *et al.* 1992). Clinical signs may not identify all the lesions in the CNS. Gearhart *et al.* (1986) described a cerebellar mass in a dog due to GME, but multifocal lesions were also found throughout the neuraxis.

In most cases, a definite diagnosis of GME can only be established histopathologically (Braund 1985, Sarfaty *et al.* 1986). Gross lesions are evident if the perivascular inflammatory reaction is

sufficient to produce a mass effect. Areas of swelling and yellow to grey discoloured nodules are found predominantly in the white matter, particularly of the cerebellomedullary region (Summers *et al.* 1995). Disseminated lesions are found more commonly than focal lesions. Microscopically, typical lesions are characterised by perivascular cuffing comprising macrophages, lymphocytes, monocytes, plasma cells, and infrequently, neutrophils, setting in nets of reticulin fibres (Braund 1985). Cordy (1979) described an epitheloid differentiation of the macrophages, forming a discrete nest within the cuff. In severe chronic cases with many thick cuffs, oedema, necrosis and glial cell reaction in the intervening parenchyma are evident due to aggregation or coalescence of the perivascular lesions (Cordy 1979, Braund 1985). The histopathological resemblance of GME to the immunopathological response of the CNS (i.e. experimental allergic encephalomyelitis) may support an immunological basis for the disease (Braund 1985, Thomas & Eger 1989), nevertheless, its aetiology remains undetermined.

The prognosis for permanent recovery is poor and although temporary improvement may follow steroid administration, relapse or deterioration soon occur and most animals die, or are euthanased, within three to six months of the initial presentation (Thomas & Eger 1989). Animals with focal GME have longer survival periods than disseminated forms (Muñana & Luttgen 1998) as well as dogs with evidence of white matter lesions in the caudal brain stem and spinal cord (Sorjonen 1990). Radiation is an effective treatment for dogs with GME, particularly those with focal form of the disease (Muñana & Luttgen 1998).

1.6.8.2 Steroid-responsive tremor syndrome (Generalised tremor syndrome/ Idiopathic cerebellitis)

Generalised tremors may be caused by congenital hypomyelination, toxicity, drug therapies, electrolyte imbalance, and an idiopathic condition referred to as generalised tremor syndrome, idiopathic cerebellitis (Cuddon 1990, Oliver & Lorenz 1993) or steroid-responsive tremor syndrome (Wagner *et al.* 1997). In this section, only the generalised tremor syndrome will be reviewed. Maltese Terriers, West Highland White Terriers and other small to medium-breed dogs such as Lhasa Apso, Bichon Frise, Spitz, Samoyed, Poodle, Dachshund, Pekingese, Beagle, Yorkshire Terrier, Australian Silky Terrier, Miniature Pinscher and other mixed-breed dogs are primarily affected (Farrow 1986, Parker 1991, Bagley *et al.* 1993, Wagner *et al.* 1997). Because the majority of affected dogs have a white hair coat, this disease is also termed "white shaker syndrome". However, non-white dogs also predominated in the study of Wagner *et al.* (1997) indicating that dogs of all colours are susceptible. The dogs are usually less than five years old and weigh less than 15 kg (Bagley 1991, Bagley *et al.* 1993, Wagner *et al.* 1997).

Clinical signs are usually of acute onset, with depression and multifocal neurological signs. The tremor typically worsens with excitement and diminishes markedly at rest or with relaxation, and ranges from mild tremors to severe generalised tremors and truncal movements that restrict the dogs' ability to stand or walk. Some dogs may be presented with depression, seizures or vestibulo-cerebellar disturbances (i.e. ataxia, tremor, hypermetria, lack of menace response, nystagmus or disconjugate, irregular jerky eye movements, head tilt, paresis) (Bagley *et al.* 1993, Wagner *et al.* 1997) but other dogs may have tremor as the only abnormal feature (Farrow 1986). Results of routine haematology and biochemistry are usually normal. CSF analysis may be normal or may reveal a mild lymphocytic pleiocytosis with normal to elevated protein concentrations. Results of CSF viral titre to CDV, adenovirus, parvovirus and CHV have been negative (Bagley 1991).

Histological examination of brain tissue has shown a mild, non-suppurative meningo-encephalomyelitis, with mild lymphocytic perivascular cuffing most apparent in the cerebellum (although not confined to the cerebellum). In some dogs, abnormal histopathological findings may not be present (de Lahunta 1983, Farrow 1986). The choroid plexus and meninges may show infiltration by lymphocytes and plasma cells. Though a definite aetiology has not been determined, an underlying immune-mediated disorder is most suspected (Farrow 1986). This syndrome appears to be a diffuse CNS process, affecting the cerebellum and cerebellar tracts more than the conscious proprioceptive or voluntary motor tracts (Parker 1991).

Most dogs respond favourably to treatment with corticosteroids at immunosuppressive dosages (prednisone or prednisolone 1-3 mg/kg by mouth, twice daily) (Bagley 1991). Tremor usually resolves within one to three weeks of continual therapy. A prolonged withdrawal schedule, over several months, may be required to prevent recurrence. Occasionally successfully treated cases will relapse months later and require reinstitution of glucocorticosteroid therapy (Farrow 1986). The use of beta-blocker propranolol may be useful in reducing tremors (Bagley *et al.* 1993). Benzodiazepines (diazepam, clorazepate dipotassium) and barbiturates (pentobarbital sodium) have been used to manage tremors in addition to steroid therapy (Wagner *et al.* 1997). Long-term prognosis for dogs having steroid-responsive tremor syndrome is excellent.

1.6.9 Toxins

Less commonly, intoxication may result in generalised tremor and ataxia suggestive of cerebellar dysfunction. Chronic low-grade lead poisoning may cause tremor, ataxia and dementia. Chronic low-dosage organophosphate poisoning from the use of flea collars and topical or systemic insecticides frequently causes tremor preceding seizures and neuromuscular weakness. Metaldehyde poisoning from snail bait causes tremor and ataxia progressing to depression and coma (Oliver & Lorenz 1993). Hexachlorophene toxicity has been reported in puppies (cited in Oliver & Lorenz 1993) and a cat (Thompson *et al.* 1987) with tremor and ataxia. Histopathological examination of the cat revealed demyelination of the white matter, with intact neuronal cell bodies. Bromethalin toxicosis in dogs and cats may develop diffuse white matter vacuolisation involving the cerebellar white matter (Dorman *et al.* 1992). Metronidazole toxicosis in dogs produces clinical signs consistent with lesions of the vestibular nuclei and/or cerebellum. Histological lesions involve central vestibular and brain stem with mild swelling of myelin sheaths of vestibular-cerebellar white matter tracts and Purkinje cell death (Dow *et al.* 1989, Fitch *et al.* 1991). Selective loss of Purkinje cells was evident in another study using nitroimidazole which is closely related to metronidazole (Dow *et al.* 1989). Some plant or fungal toxicities may present with cerebellar signs (Hoskins & Nicholson 1995). In general, these toxins cause lesions which involve the deep cerebellar white matter or Purkinje cells. This may explain the development of ataxia, dysmetria, and tremors. Furthermore, other CNS signs are usually also apparent other than cerebellar signs. Treatment is mainly by preventing further exposure, increasing excretion and supportive care.

1.6.10 Traumatic diseases of the cerebellum

1.6.10.1 Head injury

The cerebellum is very well protected in the caudal fossa by the skull, thus, it has to be a very severe cranial trauma to result in cerebellar signs. Forebrain and/or brain stem signs such as seizures or coma are usually present concurrently. However, cerebellar signs may predominate following intracranial injury if this structure has received the main impact of the injury (de Lahunta 1983). Fracture of the occipital bone causing cerebellar compression in a dog has been described (Gleeson & Larkin 1972). Severe lesions (e.g. such as experimental ablation) of the cerebellum can cause decerebellate rigidity — a posture characterised by opisthotonus, tonic extension of the thoracic limbs, alternate clonic movement of the hind limbs, a tendency to stagger and fall backwards if placed on the feet; furthermore, tendon reflexes may be exaggerated (Holliday 1980). Although the posture is similar to decerebrate rigidity which occurs with severe lesions of the brainstem or cerebrum, the decerebellate animal is conscious and has normal pupillary function. Unilateral ablation of the cerebellum will produce ipsilateral cerebellar signs. Traumatic lesions of the flocculonodular lobe may be more common. In addition to cerebellar signs, vestibular signs such as nystagmus and abnormal or absent vestibulo-ocular movement can be seen. Signs are usually acute in onset and non-progressive (de Lahunta 1980 a) unless there is ongoing haemorrhage or unstable fracture.

Radiographic evaluation of the skull may reveal fracture or penetrating injuries of the skull, ideally CT or MRI is utilised for head trauma evaluation (Hopkins 1996). Treatment include supportive therapy and surgical decompression of the cerebellum. The domestic animal is capable of remarkable compensation following extensive traumatic lesions of the cerebellar cortex (de Lahunta 1983), however, the recovery is usually incomplete (Gleeson & Larkin 1972). Lesions that involve the cerebellar nuclei produce more severe deficits making compensation less likely.

1.6.10.2 Cerebellar herniation

There are four principle forms of brain herniation seen in human beings, which can be applied to domestic animals: cingulate gyrus herniation, caudal transtentorial, rostral transtentorial, and foramen magnum (or tonsillar) herniation (Kornegay *et al.* 1983). More than one form can occur in a single animal. Among the four forms, the last two involve displacement of the cerebellum. Rostral transtentorial herniation implies rostral displacement of the rostral cerebellar vermis ventral to the membranous tentorium cerebelli, with resultant compression of

the midbrain or temporal cortex, or both. Foramen magnum herniation indicates caudal displacement of the caudal cerebellar vermis through the foramen magnum, which results in compression of the displaced cerebellum and the medulla oblongata, and thus the respiratory centres and long tracts are affected (Kornegay *et al.* 1983). The cerebellum herniates as a consequence of increased intracranial pressure which may be secondary to a space-occupying mass or intracranial hypertension. Usually the animal has cranial trauma or an underlying disease which increases the intracranial pressure, such as inflammation (i.e. encephalitis) or intracranial neoplasm. Under general anaesthesia, intracranial pressure may increase, therefore, a sudden reduction of intracranial pressure associated with CSF collection may result in foramen magnum herniation. This leads to brain stem dysfunction through neurovascular compression and distortion (Hopkins 1996). Clinical signs, which are often rapidly progressive and self-perpetuating (Kornegay *et al.* 1983), include tetraplegia, apnoea and coma. Rusbridge (1997 b, c) described a disease in Cavalier King Charles Spaniels characterised by persistent scratching of the shoulder in which cerebellar tonsillar herniation and syringohydromyelia were seen on MRI. Animals with only rostral transtentorial herniation may have no clinical signs directly attributable to the herniation due to minimal midbrain involvement, and the neurologic dysfunction due to the underlying disease is more critical.

Corticosteroids and osmotic diuretics may provide only temporary relief of the clinical signs and rapid deterioration usually follows. Herniation due to cranial trauma may be reversible by prompt use of corticosteroids, osmotic diuretics, and surgical decompression (Kornegay *et al.* 1983). However, in general, brain herniation is nearly impossible to reverse, and the animal either dies or is euthanased.

SECTION II.

CLINICAL CASES

2.1. MATERIALS & METHODS

2.1.1. Case Selection

The 25 cases presented here were selected from those admitted to the University of Glasgow Veterinary School (GUVS) during the period October 1996 to June 1998, for investigation of an abnormal gait or inco-ordination. Cases of ataxia due to involvement of spinocerebellar tract such as cervical spondylomyelopathy (wobbler syndrome) and chronic degenerative radiculomyelopathy (CDRM) were not included in the study. Only those cases which affected primarily the cerebellum are recorded.

2.1.2. Clinical Details

A detailed history was taken from the owners and the referring veterinary surgeons and relevant details were recorded. All cases underwent systemic examination and only significant abnormal findings were described.

A complete neurological examination was carried out in each case as described by Oliver & Lorenz (1993). Mental status of the animal was obtained by observing its response to environmental stimuli or to people and by questioning the owners about any change in behaviour and attitude towards other people or animals. Abnormal involuntary movements such as tremors were noted when the animal was standing or in sternal recumbency. Intention tremor was noted, when the animal sniffed the objects in the consulting room such as the legs of the table, or by offering an object or food to the animal. The posture and gait were evaluated for inco-ordination or weakness, with assistance if necessary, by allowing the animal to wander around the consultation room, and by walking on a lead in an open area. In most cases, the owners were asked to lead the animal up and down stairs, or in a tight circle to observe abnormal gait, such as dysmetria and ataxia, which were usually exacerbated by these procedures.

Conscious proprioception, unconscious proprioception and motor function were assessed by paw positioning response, tactile and visual placing reactions, reflex stepping, hip sway test, hopping, wheelbarrowing, external postural thrust, hemistanding and hemiwalking. Segmental spinal reflexes were assessed in each limb with the animal in lateral recumbency. Muscle tone was examined by passive flexion and extension of the limb. The patellar reflex, the extensor carpi radialis reflex and the pedal reflex were evaluated. The deep pain sensation and the

panniculus reflex were routinely tested. Bladder and bowel control was evaluated by questioning the owner, observation of hospitalised cases, bladder palpation and examination of perineal reflex. Hyperaesthesia of the spine caudal to the cervical region was evaluated by manual pressing, and by flexing the neck dorsally, ventrally and laterally.

Cranial nerve examination was performed in every case as described by Oliver & Lorenz (1993). In all cases, particular note was made of the presence of menace response. The pupils were assessed for size and symmetry in a dark room using distant ophthalmoscopy. Fundoscopic examination was performed, and any ocular tremor was noted. Vestibular-eye movements were elicited by moving the animal's head sideways. Spontaneous nystagmus was observed while the normal head position was maintained, while positional nystagmus was observed with the animal upside down and in lateral recumbency.

Based on the clinical findings, an attempt was made to localise the lesion to the cerebellum. Observation of the gait was a major part of the neurological examination, to decide whether the lesion was diffuse or lateralised. Thorough systemic and neurological examination may reveal that the cerebellum only forms part of a multisystem disease.

2.1.3. Ancillary Investigation

In most cases, video recording was used to record the initial presentation of gait abnormality for a comparison at the time of re-assessments. In several cases in which a non-progressive condition was strongly suspected (i.e. cerebellar developmental anomaly in cases 4, 6, 8) or the animal was showing improvement (case 24), no investigations were pursued. Instead, at least one re-assessment or telephone consultation was offered, to assess and monitor progression. However, in the majority of the cases, further diagnostic procedures were pursued to investigate the aetiology of the problem. The relevant tests were detailed with individual case reports.

Routine haematology and biochemistry were performed in most cases to investigate the possibility of systemic disease and to evaluate general health prior to general anaesthesia. Haematology includes red blood cell count, haemoglobin concentration, haematocrit, platelet count, total and differential white blood cell count. A routine biochemistry includes sodium, potassium, sodium to potassium ratio, chloride, calcium, magnesium, phosphorus, alkaline phosphatase (ALKP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, cholesterol, creatinine, urea, glucose, total protein, albumin and globulin. Creatine kinase, γ-glutamyl transferase (GGT), lactate dehydrogenase (LDH) and triglyceride were

determined in some cases. Several cases received more than one haematology or biochemistry tests. The results were compared to the reference ranges of GUVS laboratories (See Section 4.1). Serum protein electrophoresis was performed in case 11. Urinalysis was not performed in every case.

Blood samples from cases 3, 7, 10, 11, 12 and 13 were submitted to the Feline Virus Unit at GUVS for antibody titre to FCoV, FIV, and antigen titre to FeLV. Antibodies to *Toxoplasma gondii* were performed in cases 1, 3, 7, 12 & 13 by either Sabin-Fieldman dye test (Scottish Toxoplasma Reference Laboratory) or latex agglutination test (Feline Virus Unit, GUVS). Antibody titre to *Neospora canis* was performed in cases 1 and 18. Blood samples from case 1 were also taken for determination of lead and mercury levels. Thyroid function was evaluated in case 25 by assessing the canine thyroid stimulating hormone (cTSH) and free T_4 levels in serum, while only T_4 was determined in cases 11 and 12, to rule out hyperthyroidism in cats.

Radiography was performed in a number of cases to include the cervical spine (case 15, 17, 18, 19), lumbar spine (case 3), inflated chest (case 17, 25), and abdomen (case 3, 17). A bone marrow aspirate was obtained from the iliac crest in case 17 under general anaesthesia, using a disposable Klima biopsy needle (Baxter's Pharmaceuticals). The technique used was described by Relford (1991).

CSF sampling was performed under general anaesthesia. A variety of anaesthetic regimes were employed depending upon individual patient requirements. CSF samples were obtained from the cisterna magna (cerebellomedullary cistern) or lumbar cistern in some cases into sterile plastic collection tubes. The collection site was clipped and aseptically prepared. The CSF collection technique used was described by Wheeler and Sharp (1994). Cisterna magna samples were collected using a 21 or 22 gauge 1.5 inch hypodermic needle. Lumbar cistern CSF was obtained from case 13 by using a 1.5 inch 22 gauge spinal needle (Monoject 220 Spinal Needle, Diamond point, Sherwood Medical Industries, St. Louis, U.S.A.). The white blood cell count was measured within 30 minutes of collection, using a standard haemocytometer (modified Fuch's Rosenthal haemocytometer). If the white blood cell count exceeded 5 cells/mm^3, a differential count was determined following cytocentrifuge (Cytospin). Total protein concentration was determined by laboratory determination. These values were compared to the literature reference values (Bailey & Higgins 1985, Rand *et al.* 1990 a, b). Generally, the normal value for protein is < 250 mg/l from the cisterna magna and < 450 mg/l from the lumbar cistern. In cases 21, 23 and 25, antibody titre to CDV in CSF (& serum in case 25) was also determined.

From the history, clinical findings and the results of ancillary investigations, a diagnosis was made and treatment was initiated as appropriate. In cases where the prognosis was hopeless, post-mortem examination and histopathological examination were performed with the owner's permission.

2.1.4. Tissue fixation, processing and staining for histopathological examination

The details of the preparation of all fixatives, tissue processing protocols, staining protocols and stains used are given in the Appendix (Section 4.2 - 4.5).

2.1.4.1. Routine staining (Hematoxylin & Eosin) and cresyl violet

The majority of neural and non-neural tissues were fixed in 4 % buffered neutral formalin (BNF) for routine and immunocytochemical staining. Selected samples were processed using a Shandon Elliot automatic tissue processor (Histokinette) for paraffin-wax embedding and tissues were blocked out in paraffin wax at 60°C. Sections were cut on a Biocut 2035 microtome (Leica) at 8 μm for routine staining with H & E and left overnight at 60°C. Slides were mounted in DPX (BDH). In order to assess for Purkinje cell loss, sections were cut at 15 μm and stained with cresyl violet.

2.1.4.2. Resin-embedded sections and staining for light and electron microscopy

In selected cases, tissue was fixed in a paraformaldehyde-glutaraldehyde mixture (Karnovsky's modified fixative) and processed for resin-embedded sections using a Lynx *el* microscopy tissue processor (Leica). Sections for light microscopy were cut at 1 μm on a Ultracut E ultratome (Reichert-Jung), mounted on plain sulphuric acid-treated slides and stained with methylene blue/azure II. Slides were heated on a hot plate to 60°C and then flooded with stain for 10-30 seconds, followed by rinsing in running tap water. Slides were dried overnight on the hot plate and mounted in DPX (BDH).

Ultrathin sections (60 nm) were cut on a ultratome for electronmicroscopy and mounted on 200 mesh-3.06 mm diameter copper grids. They were stained with lead-citrate and uranyl acetate.

2.1.4.3. Immunocytochemistry: Peroxidase anti-peroxidase (PAP) immunostaining

Occasional immunocytochemical studies were performed as indicated in individual cases. All incubations with antibodies and links were performed in a humidifying chamber. Tissue

sections were cut on a Biocut 2035 microtome (Leica) at 6 μm. The PAP immunostaining protocol is detailed in Section 4.5.2. Immunostaining were performed with the following antibodies: SMI-31, GFAP and Calbindin-D-28K. Their sources, dilutions and links used for PAP immunostaining are summarised in Table 10 (See Section 4.5).

2.1.4.4. Prion protein immunocytochemistry

Prion protein immunocytochemistry was performed with the monoclonal primary antibody 3F4 in cases 12 and 13, for further confirmation of FSE. The protocol used for PrP immunocytochemistry has been described in Bell *et al.* (1997), and is detailed in Section 4.5.3.

2.2 CASE SUMMARIES & DISCUSSION

The following cases were grouped according to aetiology making use of the DAMNIT system. Patient details, presenting signs and the clinical or pathological diagnoses are summarised in Table 5. In those cases in which a definitive diagnosis cannot be made, a tentative diagnosis is given instead.

Table 5. Summary of patient details.

Case	Breed	Age	Sex	Diagnosis
1 (130768)	Border Collie	13 m	M	Cerebellar degenerative disease
2 (131417)	Domestic Short haired cat	3 y	MN	Cerebellar degenerative disease
3 (131906)	Domestic Long haired cat	4 m	M	Lysosomal storage disease
4 (130665)	Short haired Colourpoint	6 m	M	Cerebellar hypoplasia (T)
5 (132371)	British Blue	1 y	MN	Cerebellar hypoplasia (T)
6 (132745)	Domestic Short haired cat	5 m	M	Cerebellar hypoplasia (T)
7 (133500)	Domestic Short haired cat	3.5 y	MN	Cerebellar hypoplasia (T)
8 (132383)	Jack Russell Terrier cross	1 y	F	Anomalous cerebellar disorder
9 (133247)	English Springer Spaniel	6.5 y	M	Paradoxical vestibular syndrome (neoplasia) (T)
10 (131616)	Domestic Short haired cat	8 m	M	Feline Infectious Peritonitis (FIP)-dry form
11 (132764)	British Short haired cat	9 y	F	FIP dry form
12 (131333)	Domestic Short haired cat	9.5 y	F	Feline spongiform encephalopathy (FSE)
13 (134380)	Domestic Short haired cat	6.5 y	MN	FSE
14 (130321)	Yorkshire Terrier	5 y	F	Steroid-responsive tremor syndrome (SRTS)
15 (132423)	Yorkshire Terrier	3 y	F	SRTS
16 (132499)	West Highland White Terrier	1.5 y	M	SRTS
17 (132692)	West Highland White Terrier	5 y	F	SRTS
18 (133813)	Miniature Poodle	3 m	F	SRTS
19 (133880)	Yorkshire Terrier	2.5 y	M	SRTS
20 (133905)	West Highland White Terrier	15 m	FN	SRTS
21 (134359)	English Springer Spaniel	18 m	M	SRTS
22 (134669)	Maltese Terrier	5 y	FN	SRTS
23 (134725)	West Highland White Terrier	20 m	F	SRTS
24 (132809)	Domestic Short haired cat	4 y	FN	Trauma or angiopathy (T)
25 (134457)	German Shepherd Dog	8.5 y	M	Transient paradoxical vestibular syndrome (Inflammatory or angiopathy) (T)

Key: y: year, m: month, M: male, F: female, N: neutered, T: tentative diagnosis

2.2.1. DEGENERATIVE CEREBELLAR DISEASES

Three cases presented to GUVS were classified as cerebellar degenerative diseases using the DAMNIT system. The first two are examples of abiotrophies and the third case is a LSD. They are discussed separately in detail.

Case 1: No. 130768

Signalment: Shep, 1 year old neutered male Border Collie, body weight (BW) 20 kg

The dog was presented with a history of progressive hind limb ataxia. The owners noticed a mild hind limb gait abnormality when he was ambulatory, however, they were uncertain whether this was "puppy behaviour" or a genuine problem. They were more convinced that there was a problem when the dog was 5 months old because of his difficulty in going up and down stairs. The dog was otherwise healthy.

On examination, the dog was alert and bright but ataxic in all limbs, the hind limbs being more severely affected than the fore. He had a wide-based stance and marked truncal ataxia, which was characterised by swaying of the body. The gait was hypermetric, which was exacerbated while going up- or downstairs. Other abnormalities included a bunny-hopping gait while going downstairs, crossing of the hind limbs when turned in tight circles, and occasional falling over to either side. A very mild tremor was noticed by observing the tips of his ears. No obvious intention tremor was observed. A diffuse cerebellar disease was suspected.

The dog was re-examined a month later to determine whether the clinical signs progressed. The owner reported that the clinical signs seemed slightly worsen, i.e. when going up stairs the dog lost balance and fell over more frequent. He often squatted to avoid falling while passing urine. The cerebellar ataxia and hypermetria were more severe compared to the last examination. The head tremor had become much more obvious during rest and was exacerbated by excitement. Intention tremor was observed by offering Shep an object; he bobbed his head and his nose bumped into the object frequently. Postural reactions were initiated slowly and exaggerated, hypermetric responses were made.

Routine haematology revealed mild neutrophilia and biochemistry was unremarkable. Analysis of CSF sampled from the cisterna magna showed a protein level of 190 mg/l. The cell count was not determined due to blood contamination. The blood lead level was within normal limits (0.08 μg/ml, normal <0.35 μg/ml). Blood mercury level and Toxoplasma and Neospora

serology were negative. The most likely diagnosis was a cerebellar degenerative disease such as cerebellar abiotrophy or a lysosomal storage disease.

The dog was re-assessed two months following the tentative diagnosis. The owner reported continuous deterioration. He started to drag his hind limbs after 10 to 15 minutes walking. Mild hind limb muscle wastage of the hindquarters was also noticed. On examination, there was marked progression of the disease with increased spasticity, generalised ataxia, and hypermetria. Slight ventrolateral positional strabismus of the left eye was noticed upon neck extension. During the next 6 weeks, the dog continued to deteriorate in relation to dragging of the hind limbs, and the cerebellar signs. His poor co-ordination frequently resulted in bumping into objects, falling over and occasionally hurting himself. The owners elected for euthanasia and a necropsy was performed.

Pathology

Gross examination revealed mild atrophy of the cerebellum. The sulci appeared to be very prominent. Within the cerebellar cortex, there were overall loss of Purkinje cells, affecting all lobes of the cerebellum (Figure 8). The cell loss was patchy and additionally, in affected regions, there was proliferation of glial cell nuclei, most probably Bergmann glia. The molecular and granule cell layers appeared largely intact. The deep cerebellar white matter, and to a lesser extent, the cerebellar folia, was abnormal. There was a generalised gliosis, comprising microglia, and hypertrophied astrocytes. In addition, numerous axonal swellings were present and some evident of axonal degeneration was observed. Within the deep cerebellar nuclei and lateral vestibular nuclei, a prominent gliosis was evident. Axonal swellings were also detected in these nuclei (Figure 9).

Although the optic nerve, chiasm, and tracts appeared normal, changes were present within the rostral colliculi, an area of termination for the optic tracts. The stratum griseum superficiale and stratum opticum of the rostral colliculi contained axonal swellings and a moderate gliosis (Figure 10).

A number of swollen axons were present in the gracile and medial cuneate nuclei. Although axonal swellings in these nuclei become more common in old dogs, they are very uncommon in a 1-year-old dog. Sections of the spinal cord and associated nerve roots at multiple levels showed no abnormalities.

Immunostaining with SMI-31 showed immunopositive axonal swellings in the deep cerebellar white matter, and occasionally within the granule cell layer (Figure 11). Immunostaining of

GFAP showed a moderate increase staining of the cerebellar white matter and nuclei. Immunostaining with Calbindin-D showed that the axonal swellings were intensely positive (Figure 12).

Discussion

The history and the series of clinical examinations were consistent with a progressive cerebellar disorder, and the most likely diagnosis was a degenerative disease, i.e. cerebellar abiotrophy or LSD. Ceroid lipofuscinosis has been reported in Border Collies (Taylor & Farrow 1988, Studdert & Mitten 1991, Jolly *et al.* 1994). The onset of clinical signs was usually at 16 to 23 months, which was later than in the present case in which the clinical signs were present probably before 5 months of age. Moreover, the major clinical signs in Border Collies affected with ceroid lipofuscinosis were behavioural changes, motor abnormalities (including cerebellar ataxia and minor proprioceptive deficits) and blindness which often developed in this order (Studdert & Mitten 1991). The behavioural changes included hyperactivity, with compulsive running or aimless wandering, were commonly observed initially, and progressed to loss of learned behaviour including house-training, confusion, exaggerated response to auditory, visual or tactile stimuli, continued barking, frenzy, mania and rage. Shep showed no behavioural changes or blindness during the disease course, suggesting that ceroid lipofusinosis is unlikely. In addition, there was no storage material within neurones microscopically.

Cerebellar folia degeneration and atrophy has been described in Rough-coated Collies (Hartley *et al.* 1978) and a Border Collie (Gill & Hewland 1980), showing progressive cerebellar ataxia at 4 to 8 weeks of age. A suspected inherited cerebellar neuroaxonal dystrophy has also been described in Border Collies which developed cerebellar dysfunction at 2-4 months of age (Clark *et al.* 1982). Clinically, Shep showed similarities to these dogs, however, there were several major differences between the pathological findings. In the Rough-coated Collies, the anterior folia of the vermis was markedly atrophied, which was not present in Shep. The initial lesion in the Rough-coated Collies appeared to be a massive destruction of granule cells in the anterior cerebellar vermis which was associated with, or followed by, extensive loss of Purkinje cells, Wallerian-type degeneration affecting the cerebellar white matter and all but the gracile and cuneate fasciculus in the spinal cord. There was also loss of cerebellar deep nuclei and lateral vestibular nuclei associated with gliosis and scattered spheroids. The most striking differences between Shep and the Rough coated Collies were the intact granule cell layer and a more generalised degeneration affecting all lobes of the cerebellum in Shep. It is possible that the degeneration started in a specific lobule initially. Although there was a prominent gliosis

within the deep cerebellar nuclei and lateral vestibular nuclei, and the presence of axonal swellings, the large neurones appeared largely intact in the present case. The numerous axonal swellings observed in Shep were not present in the Rough-coated Collies.

Microscopically, the Border Collies reported by Clark *et al.* (1982) had numerous axonal swellings which were almost entirely confined to the central cerebellar white matter, adjacent peduncular and folia white matter, and associated cerebellar deep and lateral vestibular nuclei; this was associated with mild Wallerian degeneration. In addition to this, axonal swellings were also present in the rostral colliculi, gracile and medial cuneate nuclei in Shep. Moreover, there was a patchy loss of Purkinje cells in the present case, while the Purkinje cells appeared normal in the Border Collies described by Clark *et al.* (1982), which may indicate that these two diseases are different from each other. However, Purkinje cell loss in neuroaxonal dystrophy were evident in other breeds such as the Rottweiler (Evans *et al.* 1988).

The pathological findings of patchy Purkinje cell loss, empty baskets, mild multifocal gliosis at the interface of the granular and molecular layers (Bergmann's gliosis) and numerous torpedoes are indicative of an ongoing degeneration and loss of Purkinje cells (Brenner *et al.* 1997). This finding correlates well with the presence of numerous spheroids and gliosis in the cerebellar deep nuclei. Although various degenerative cerebellar diseases may present similarly clinically, their differentiation at present depends on pathological findings. Many cerebellar degenerations in various species have an inherited basis and, although impossible to prove, this may be true in Shep's case.

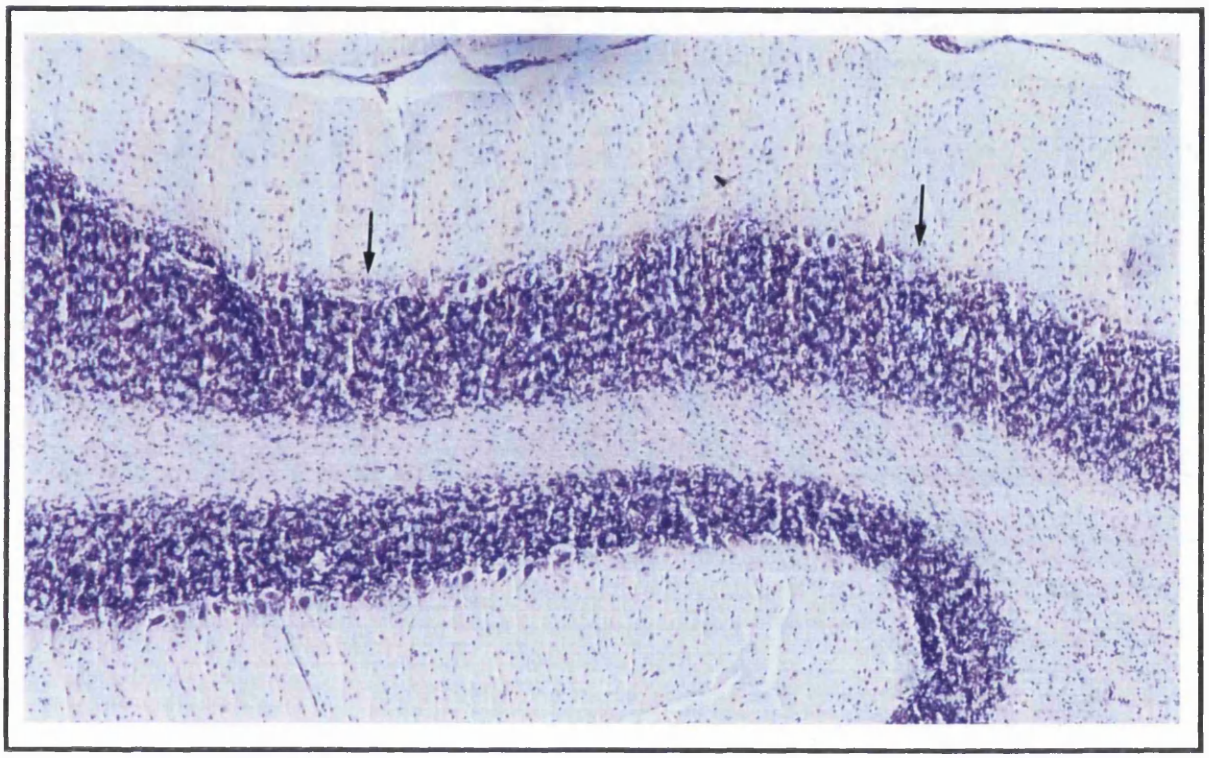

Figure 8.

Case 1. Cerebellum, showing patchy loss of Purkinje cells and proliferation of Bergmann glia (arrow). (Cresyl violet, x 70)

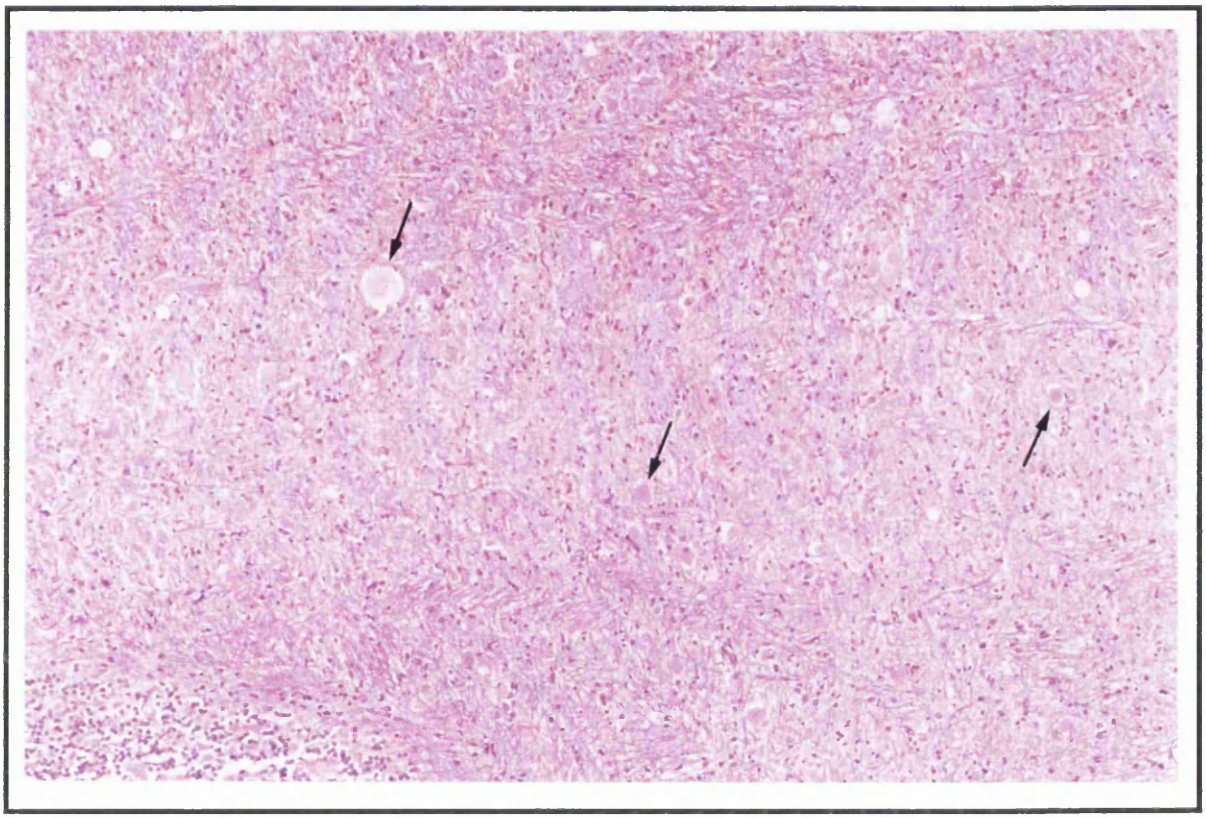

Figure 9.

Cerebellar white matter, showing axonal swellings (arrow) and generalised gliosis. (H&E, x 110)

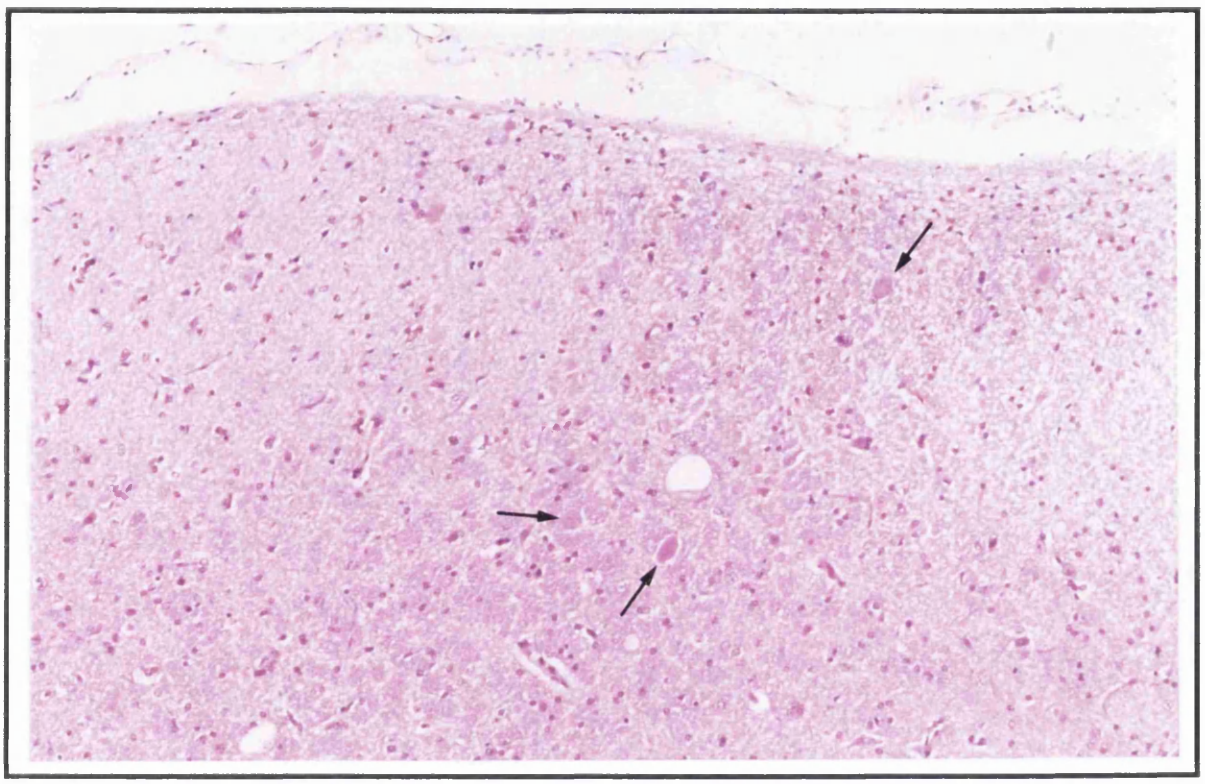

Figure 10.

Stratum griseum superficiale and stratum opticum of the rostral colliculus, showing axonal swellings (arrow) and mild gliosis. (H&E, x 145)

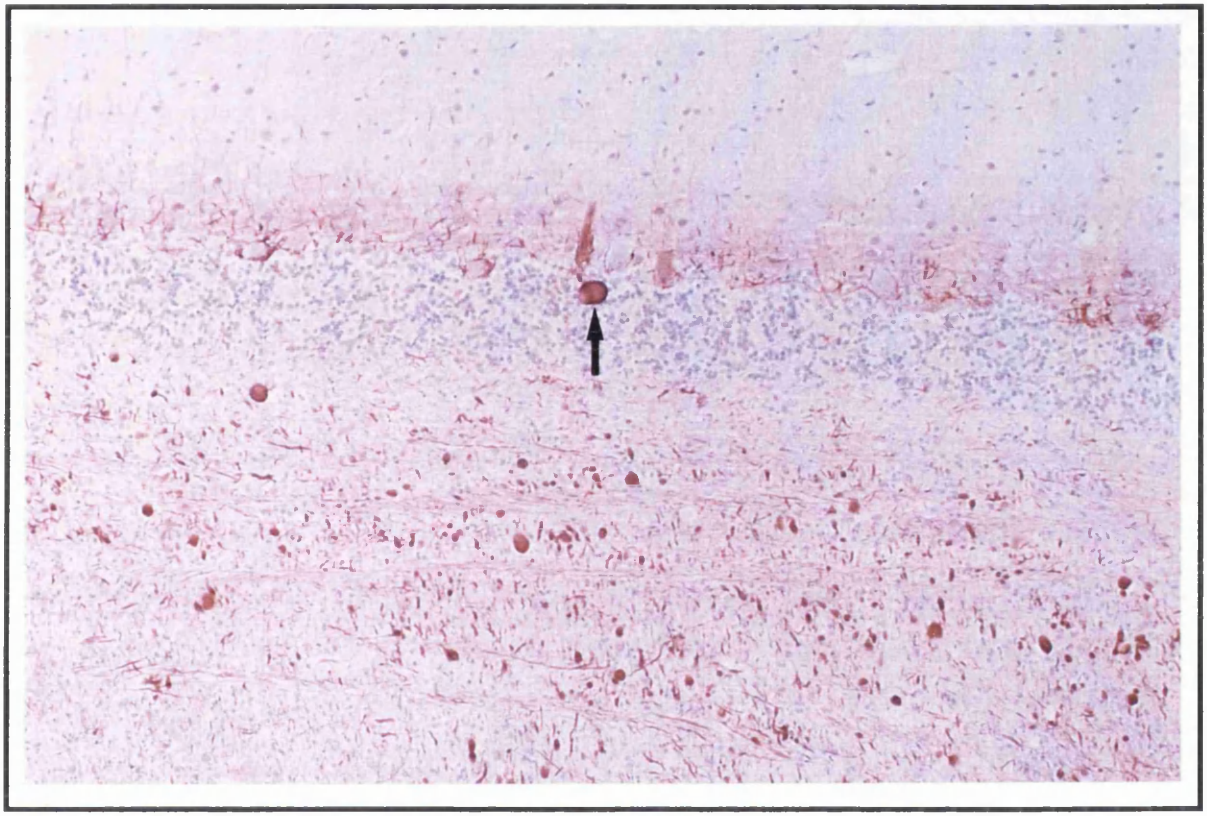

Figure 11.

Cerebellar cortex and deep cerebellar white matter. A large axonal swelling (arrow) is present on the Purkinje cell axon. Numerous other swellings are present in the white matter of the folium. (SMI-31, x 110)

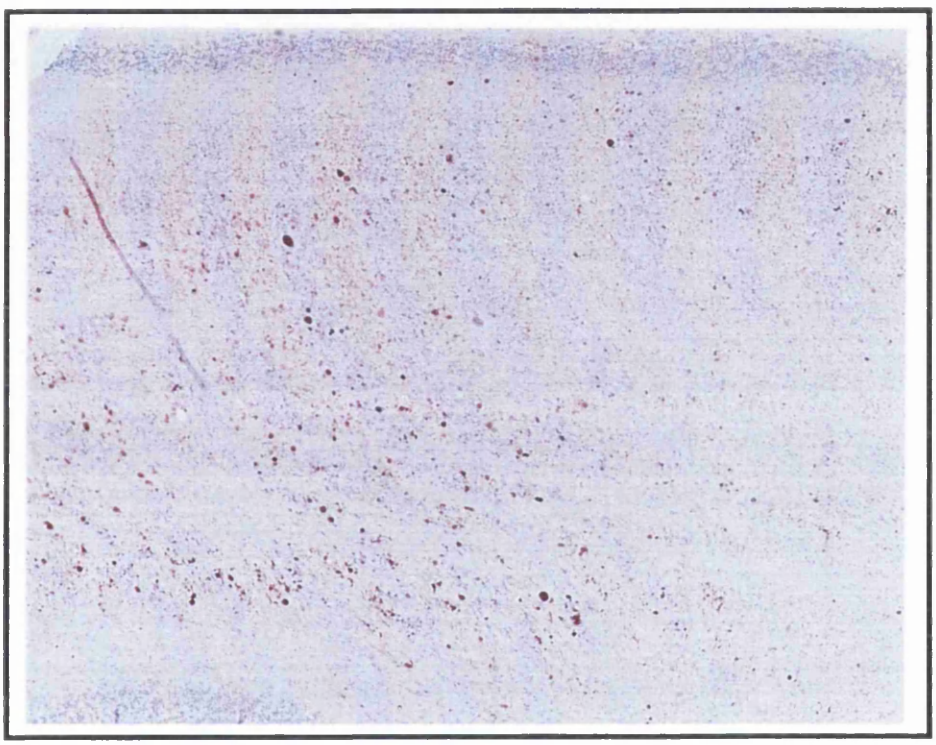

Figure 12.

A low power view of the deep cerebellar white matter to show the numerous axonal swellings. (Calbindin-D, x 44)

Case 2: No. 131417

Signalment: Wobbles, 3 year old neutered male Domestic Short-haired cat, BW 4 kg

This cat was presented to GUVS with the chief complaint of imbalance. The owner reported that the cat was apparently normal when he was 2 months old. At 3 months of age, he had an accident and dragging of his left hind limb was noticed thereafter. The condition progressed such that the cat could no longer walk in a straight line, instead he staggered and fell frequently. The owner had 3 other cats in the house and they were clinically normal. The owner also noticed that the cat tended to sleep more and his behaviour was altered, e.g. the cat began to bite people.

Observation revealed marked intention tremor and head bobbing when the cat sniffed objects. The cat developed a crouched posture and wide-based stance with severe truncal ataxia in which he swayed from side to side, forward and backward to initiate a step. He fell over and had great difficulty in righting himself. The gait was severely ataxic and hypermetric. Neurological examination revealed normal conscious proprioception. Hopping was slow in onset with an exaggerated response. Menace response was variable. The cat also had large circular movements of the head.

Clinical abnormalities were confined to the cerebellum. Differential diagnoses included cerebellar degeneration, LSD, and FSE. The cat was donated to the GUVS. Reassessment was performed twice per month thereafter for 5 months.

The cat was bright, alert and responsive during all examinations. Quite often, single jerky movement of the body was noticed in response to noises from outside the examination room. He often stretched his neck in a large circle and then fell over to either side. Menace responses were observed consistently. In general, the cat did not develop other signs in addition to the cerebellar signs.

Before the cat was euthanased, blood was taken for haematology, biochemistry and leukocyte lysosomal enzyme assay. The results of haematology and biochemistry were normal. Leukocyte lysosomal enzyme activities were normal for feline leukocyte β-galactosidase, specific hexosaminidase A, and α-mannosidase. A necropsy was performed.

Pathology

Grossly, the cerebellum appeared slightly smaller than normal. Histopathologic examination showed a generalised reduction in all layers of cerebellar cortex with narrowing of the molecular layer and a reduced number of cells in the granule cell layer. However, the most

striking appearance was a very severe depletion of Purkinje cells, such that only very occasional cells were observed (Figure 13). Immunostaining with SMI-31 showed empty baskets where Purkinje cells had disappeared (Figure 14). Concurrent with this, there was a proliferation of Bergmann glia (Figure 15) and occasional ectopic Purkinje cells were observed in the granule cell layer. In the cerebellar white matter, occasional axonal swellings were noticed, and some vacuolation and mild gliosis were seen. Very occasional degenerative fibres were observed in the brain stem and ventral spinal cerebellar tract. There was minimal vacuolation in the nuclei of the trapezoid body.

Examination of the spinal cord at several segmental levels revealed very occasional degenerative fibres in the white matter. No obvious tract specificity was shown. In addition, homogenous swellings were noted in the grey matter, more specially in the dorsal horn although all levels of grey matter were affected (Figure 16). The majority of swellings were not associated with glial response, although occasionally one was present. Immunostaining with SMI-31 showed strong staining in some swellings but not in the others suggesting that these swellings were derived from axons (Figure 17). No abnormalites were detected in the nerve roots, spinal ganglia or sciatic nerves.

Discussion

The history and clinical signs were consistent with a degenerative cerebellar disorder. Developmental anomalies or cerebellar hypoplasia caused by panleukopaenia virus is non-progressive in nature. The clinical signs in the present case was slowly progressive for at least 2.5 years; this would be extremely unlikely for infectious or inflammatory diseases, neoplasia, and most LSD.

Degenerative cerebellar disease in cats has been reported in only a few reports compared to those described in many different breeds of dogs (See section 1.6.1.2.). Schut (1946) described olivopontocerebellar atrophy in an adult cat which showed degenerative changes in the cerebellar cortex (degenerate and Purkinje cell loss, reduced molecular and granule cell layers), brain stem and pontine nuclei associated with the cerebellum. However, no histopathological examination was performed on the spinal cord.

Kelly & Gaskell (1976) described spongy degeneration in Egyptian Manu kittens which showed poor weight gain, ataxia and hypermetria since 7 weeks old. These kittens developed seizures, depression episodes and reduced activity over the next 2 months. Widespread vacuolation of white and grey matter of the brain and spinal cord was evident and electron microscopy revealed intra-myelinic vacuolation. This condition was different from the present

case based on the pathological findings, although the clinical finding of cerebellar ataxia was similar.

Neuroaxonal dystrophy has been described in shorthaired cats (Woodard *et al.* 1974, Carmichael *et al.* 1993) and Siamese kittens (Rodriguez *et al.* 1996). The clinical features were characterised by progressive ataxia, head bobbing and hypermetria since 5 weeks of age. In addition, proprioceptive deficits, paraparesis or paraplegia, cranial nerve signs (impaired vision or blindness, slow pupillary reflex, abnormal vestibular eye movements) were evident. In the report of Woodard *et al.* (1974), the ataxic kittens also had an abnormal coat colour. Histopathological findings were characterised by marked ballooning of nerve cell processes (axonal swellings) within specific regions of the brain stem and atrophy of the cerebellar vermis, loss of Purkinje cells, reduction of granule cell layer, and Bergmann's gliosis. Therefore, the present case is distinguishable from feline hereditary neuroaxonal dystrophy due to the absence of several characteristic clinical signs and pathological findings.

Cerebellar cortical atrophy has been described in mixed breed kittens by Taniyama *et al.* (1994) and Inada *et al.* (1996), in which the clinical and pathological findings in the cerebellum were similar to the present case. The Bergmann's gliosis (shown by immunostaining for GFAP) in the molecular layer is a compensatory reaction to axonal loss following the disappearance of Purkinje cells. Purkinje cell depletion will then result in reduction in granule cells and the presence of empty baskets. Nonetheless, degenerative changes in the spinal cord were also detected in the present case, which were absent in the report of Taniyama *et al.* (1996) or Inada (1996). This may due to the early euthanasia of the kitten (3-12 months) compared to the present case (3 years). The aetiology of cerebellar cortical atrophy is still unknown, although Inada *et al.* (1996) showed, via experimental breeding, that an autosomal recessive mode of inheritance was involved in related cats with cerebellar degeneration. In the study of feline hereditary cerebellar cortical atrophy, Aye *et al.* (1998) have used electron microscopy to demonstrate swelling of the distal dendrites of Purkinje cells and clusters of presynaptic boutons without any synaptic contact in various part of the cerebellar vermis. Their findings also indicate that degeneration of Purkinje cells started at the most distal part of the dendrite, and that presynapses, axon terminals of the granular cells and basket cells can exist for a long time even after complete degeneration of the Purkinje cells. This may explain the pathology findings of the cerebellum in the present case.

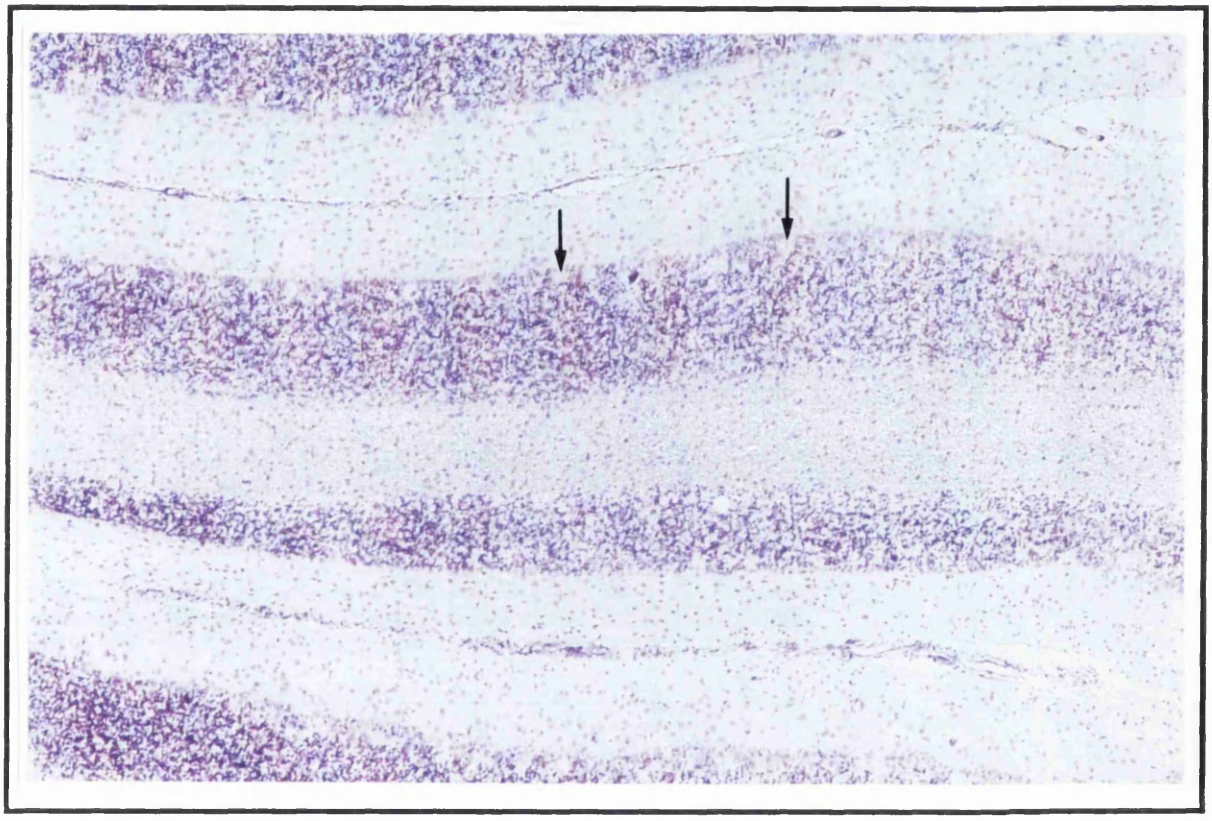

Figure 13.

Case 2. Cerebellum, showing severe depletion of Purkinje cells (arrow) and proliferation of Bergmann glia. (Cresyl violet, x 70)

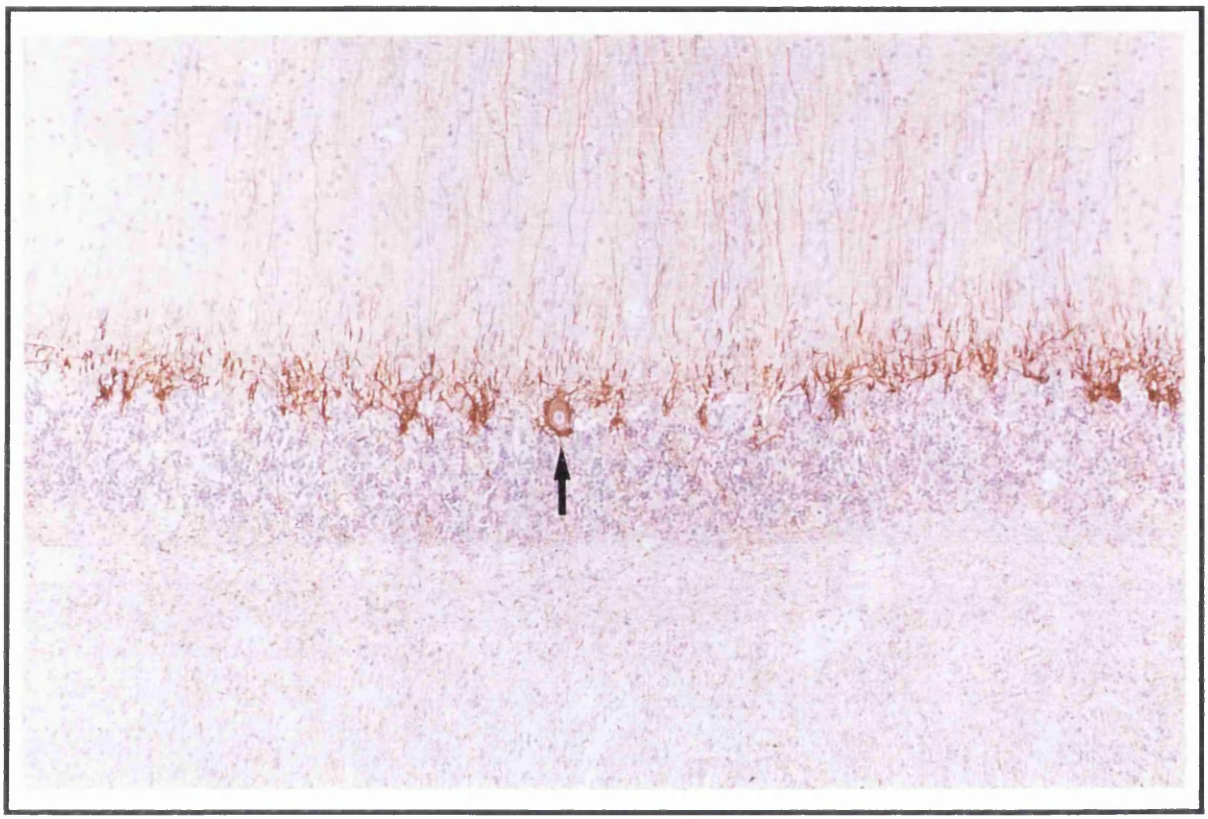

Figure 14.

Cerebellum, showing empty baskets where Purkinje cells have disappeared. Only one intact Purkinje cell is present (arrow). (SMI-31, x 110)

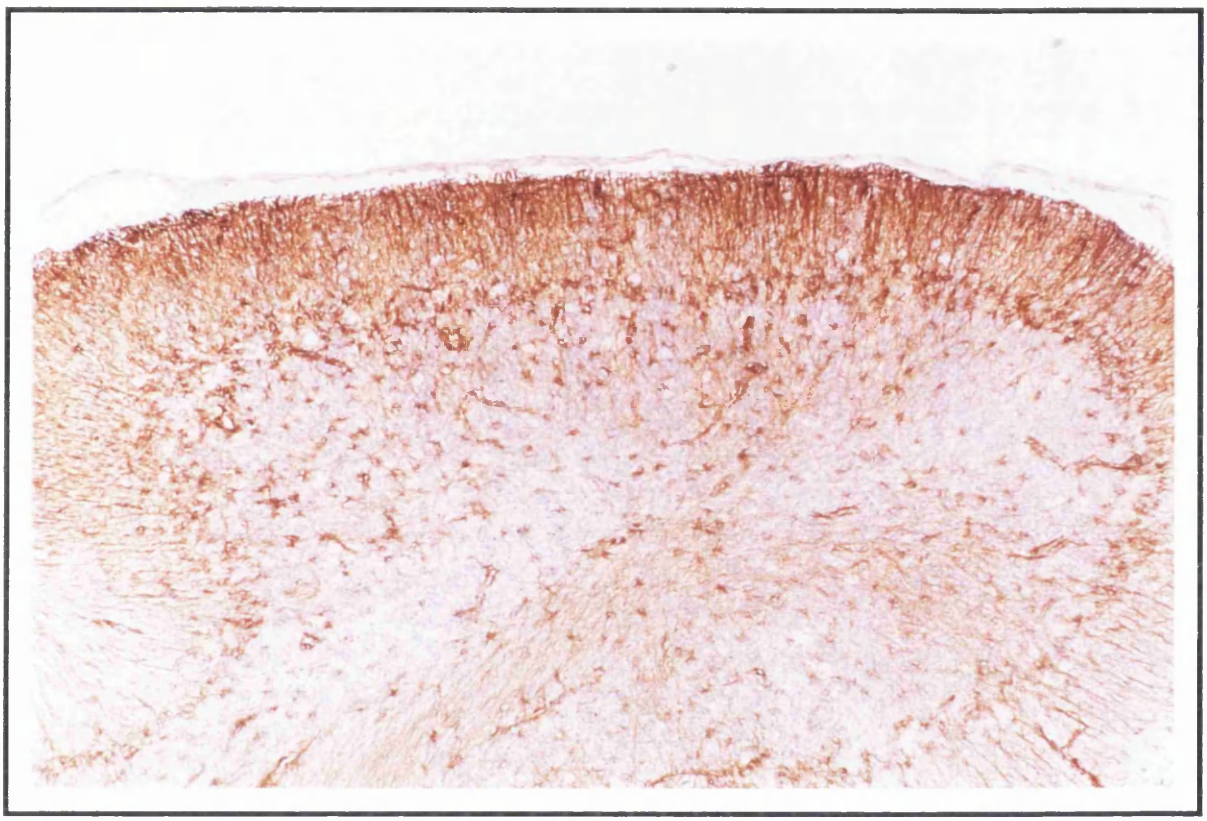

Figure 15.

Cerebellar cortex, stained with the astrocyte marker, GFAP, to demonstrate the increased number of Bergmann glia in the Purkinje cell and molecular layers. (GFAP, x 110)

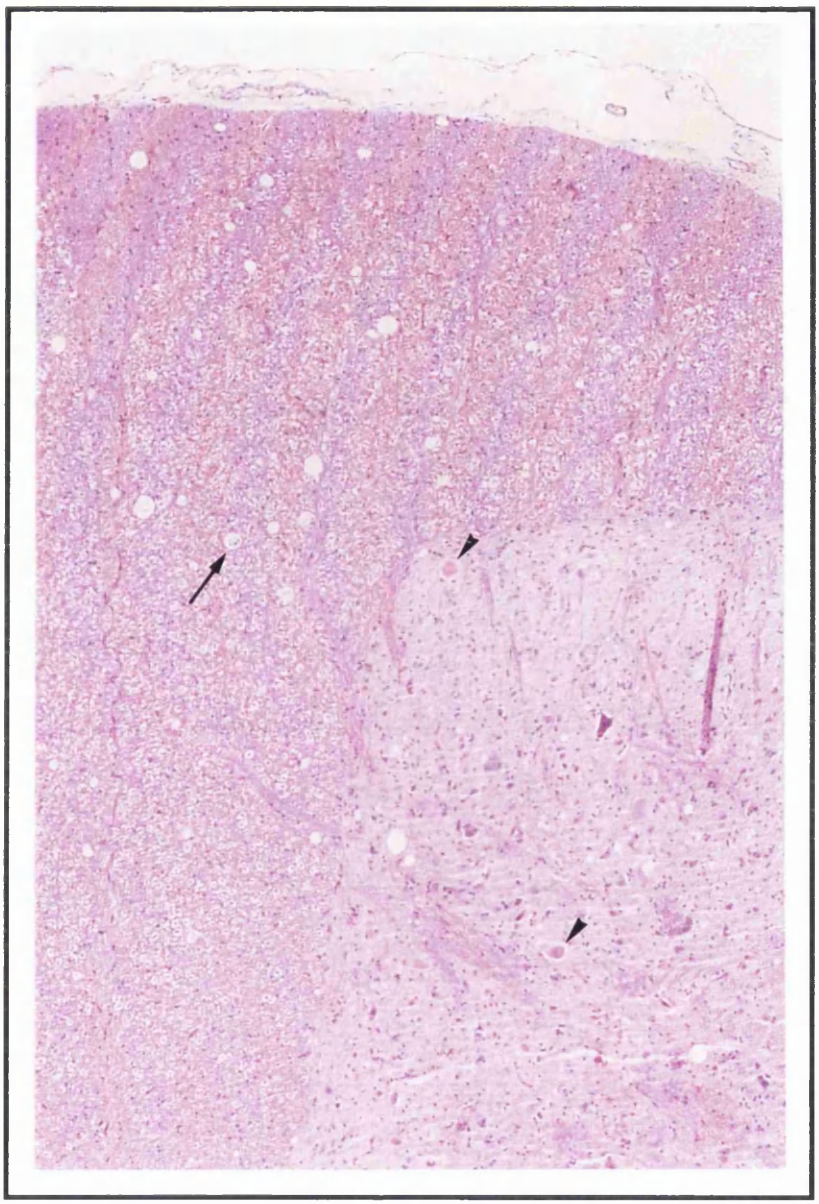

Figure 16.

Dorsal funiculus of the lumbar spinal cord. Occasional scattered degenerating fibres (arrow) are present in the white matter. Some axonal swellings (arrow head) are present in the dorsal horn. (H&E, x 70)

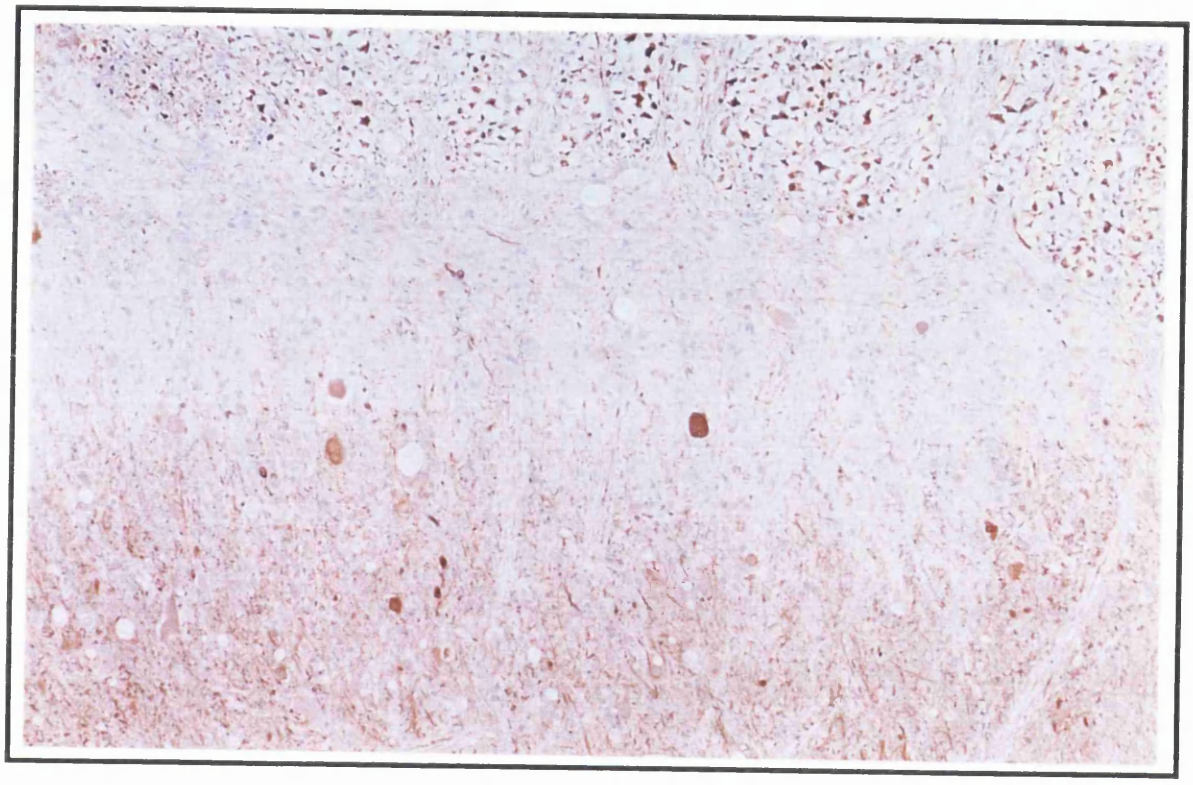

Figure 17.

Dorsal grey matter of lumbar spinal cord, showing axonal swellings. (SMI-31, x 145)

Case 3: No. 131906

Signalment: Smokey, 4.5 months old male Domestic Long-haired cat, BW 1.75 kg

This cat was presented to the GUVS with a history of sudden-onset neurological signs 2 weeks previously. The owner reported that the cat was normal before the onset of the problem. He was the last cat of the litter of three. He was kept as an indoor cat and the only cat, and had never been vaccinated. The signs included progressive wobbliness and falling over to both sides. The cat was still very lively and had a good appetite. The owner also noticed the cat's eyes were "duller" than usual.

A general physical examination was unremarkable. The cat was bright, alert and responsive. Neurological examination revealed generalised cerebellar ataxia, hypermetria, wide-based stance, generalised tremor, intention tremor, and absence of menace response bilaterally. Aqueous flare and mild photophobia were evident, and fundoscopic examination was difficult due to the presence of the aqueous flare. The cat was not bumping into things and it could track objects accurately, indicating that vision was not impaired.

Considering the history and the clinical signs of a progressive cerebellar disease in a young kitten, differential diagnoses include infections due to FIP, FIV, FeLV, toxoplasmosis, a degenerative disease such as LSD, and neoplastic disease such as lymphosarcoma.

Cisterna magna CSF analysis revealed normal cell count (0 WBC/mm^3) and protein level (80 mg/l). FIV antibody and FeLV antigen titres were negative, while the FIP profile did not suggest infection: FCoV antibody titre at 1:80, albumin to globulin ratio was 1.48, and AGP (α1-acid glycoprotein) was within normal range. Toxoplasma total antibody was not significant (less than 8 i.u./ml). Biochemistry revealed lipaemia with a markedly elevated urea (17.4 mmol/L), mildly increased cholesterol (6.82 mmol/L), and markedly elevated ALKP (2355 U/l), ALT (147 U/l), AST (38 U/l). Radiography of the abdomen did not show hepatomegaly. Urine analysis and sedimentation examination were suggestive of urinary tract infection. *Staphylococcus epidermidis* was cultured from the urine sample, the profuse culture indicated the presence of cystitis. Repeated biochemistry revealed lipaemia with markedly elevated urea (15.2 mmol/l), ALKP (858 U/l), ALT(104 U/l), AST(61 U/l), and CK (1135 U/l). Haematology was unremarkable. While waiting for the results of the leukocyte enzyme analysis (tested for GM1 type I, GM2 B-variant and O-variant form, sphingomyelinosis and α-mannosidosis), the kitten was discharged with topical Dexamethasone 1% eye-drops (Maxidex®, Alcon Laboratories (UK) Ltd.) 4 times daily (the drops alleviated the aqueous flare slightly during hospitalisation). Synulox™ (Clavulanic-potentiated amoxycillin, Pfizer Ltd.) was also

prescribed to treat the urinary infection. The leukocyte lysosomal enzyme analysis revealed enzyme activities within normal ranges.

The cat was returned for re-assessment about a month after the first visit. The owner reported progressive deterioration and the cat could not get into the litter-tray due to severe inco-ordination. Along with the cerebellar signs, the cat developed behavioural changes, in which he became very timid and frightened, vocalised a lot and did not like to be touched. During the past week, the owner also noticed that the cat was anorexic, dull and depressed, and not interested in playing anymore.

Clinical examination revealed a dull, stunted, very thin kitten. Neurological examination revealed severe cerebellar signs. The kitten had great difficulty in walking due to severe hind limb ataxia, in which the legs slid away from the body when the cat took a step forward. It used the tail to assist balance. The kitten was very irritable, with an exaggerated acoustimotor response (i.e. hissing and attacking invisible or nearby inanimate objects when his name was called) and also reacted aggressively when he was being touched.

Considering the progress of the disease, and the poor prognosis, the owner elected euthanasia. Blood samples taken before euthanasia revealed azotemia, and marked elevation of the liver enzymes (ALKP 2017 U/l, ALT 158 U/l, AST 46 U/l), however, CK value was within normal range. Repeated Toxoplasma titre was negative.

Aqueous humour drawn from the anterior chamber after death revealed a Toxoplasma antibody titre of 108 (IgG, latex agglutination test), however, the same test performed on plasma revealed a negative Toxoplasma titre. This probably indicated that the kitten was exposed to *Toxoplasma gondii* previously but it had minimal significance in contributing to the clinical signs. Although an antemortem diagnosis could not be made, from the tests performed, FIP, FIV, FeLV and toxoplasmosis were not likely. Therefore, the most likely diagnosis was LSD, although the enzyme analysis of the four common LSD of the domestic cats were within normal limits, it could still be an LSD that was not tested for.

Pathology

Gross necropsy was unremarkable. The following tissues were processed for histopathologic examination: brain, spinal cord, spinal ganglia of the cervical and lumbar spinal cord, sciatic nerve, eyes, heart, liver, spleen, kidney, lungs, and muscles. The neurones throughout the CNS were distended by accumulations of storage material within the cytoplasm (Figure 18). Although generalised, this was observed most easily in large neurones such as the ventral horn

cells, motor nuclei of the brain and Purkinje cells. The neuronal perikarya were swollen and often spherical. The nuclei were eccentric. The majority of the cytoplasm contained homogeneous or slightly granular material which had displaced the Nissl granules. The cell bodies of the glia were not distended with a similar material. Although the majority of neurones appeared to be present, albeit abnormal, occasional microglial stars suggestive of neuronophagia were present in all regions of grey matter (Figure 19). Additionally, a gliosis was present in the grey matter although its intensity varied between regions. It was very prominent, for example, in the deep cerebellar nuclei. The gliosis consisted of increased numbers of microglia and reactive astrocytes (Figure 18).

The white matter appeared largely intact with no evident of generalised demyelination. However, swollen axons were noted frequently and evident of occasional axonal degeneration was seen (Figure 20). White matter changes were, again, most obvious in the cerebellum. A section was selected at a single level of cerebellum and deep cerebellar nuclei and brain stem for immunostaining with SMI-31 to further investigate the nature of the axonal swellings. Immunostaining with SMI-31 showed multiple immunopositive axonal swellings in the Purkinje cell axons within the granule cell layer (torpedoes) (Figure 21), and in deep cerebellar white matter (Figure 22). In addition, a lesser number of axonal swellings were observed in the caudal cerebellar peduncle, and olivary nuclei. Occasional perivascular spaces of blood vessels in the brain contained lipid-filled macrophages.

Within the peripheral nervous system (PNS), the neurones of the spinal ganglia also contained storage material (autonomic ganglia were not examined). The myelinated nerve fibres appeared normal. The storage material within the CNS stained negative with PAS, muci-carmine and Alcian blue.

On electron microscopy, the neuronal inclusions were composed of moderately electron-dense multi-lamellar structures (Figure 23). These inclusions were also seen in the axons (Figure 24).

Outwith the CNS, the retinal ganglion cells were enlarged (Figure 25), by faintly PAS positive material. There were multiple corneal intrastromal spaces staining positively wholly or peripherally with Alcian blue (Figure 26). The renal tubular cells were also distended by foamy material (Figure 27).

Discussion

Young kittens presented with cerebellar signs require careful investigation to confirm whether the disease process is static or progressive. Developmental anomalies such as cerebellar

hypoplasia or other forms of malformation are present since ambulation and remain static over time. Progressive cerebellar signs may result from LSD, infectious diseases such as FIP or *Toxoplasma gondii*, other encephalitis, diffuse lymphosarcoma and chronic intoxication. Clinically, the cat was bright and lively, which was a very unusual presentation for infection, neoplasia or intoxication. Infections and encephalitides were ruled out by a normal CSF tap and negative serology. If available, CT or MRI may be useful in ruling in or out neoplasm.

Antemortem diagnosis of LSD including lysosomal enzyme analysis can be performed on serum, plasma, leukocytes, or skin fibroblast culture. Other than the four leukocyte lysosomal enzymes that were tested (GM1 type I, GM2 B-variant and O-variant forms, sphingomyelinosis, mannosidosis), other LSD can produce a similar clinical picture. They include GM1 type II, GM2 AB-variant form, globoid cell leukodystrophy, and ceroid lipofuscinosis. GM1 gangliosidosis type I involves the viscera, skeletal system and CNS, in contrast, type II has delayed-onset CNS dysfunction, variable visceral involvement, and no skeletal abnormalities. In the present case, no facial dysmorphia or skeletal deformities were detected clinically or on radiography, which makes GM1 Type II more likely. GM2 AB-variant form has not been reported in cats, and shorthaired cats with globoid cell leukodystrophy usually developed progressive cerebellar signs from 5-6 weeks old (Johnson 1970). Ceroid lipofuscinosis has been reported in Siamese and domestic cats presented with visual deficits, hyperaesthesia, seizures (Green & Little 1974, Bildfell *et al.* 1995), and in a Japanese domestic cat with shivering and difficulty in walking (Nakayama *et al.* 1993).

Although the cat initially showed primarily cerebellar signs, it developed behavioural changes and exaggerated acoustimotor response when the disease progressed, which were suggestive of multifocal CNS involvement. This is a common finding in many animals with LSD. Microscopically, virtually all neurones throughout the neuraxis were affected, indicating that the disease was a multisystem disorder. The reason why cerebellar signs are observed before other signs (i.e. cerebral or brain stem) in most LSD was not clear. Perhaps the Purkinje cells are more sensitive to changes and more vulnerable than the other neurones.

Histopathological findings correlated well with the clinical findings. The liver and the kidney contained storage materials which may explain the elevations of liver and renal enzymes. In the present case, the neurones contained non-pigmented storage materials, which ruled out ceroid-lipofuscinosis in which the neurones contain granular cytoplasmic pigment and the granules vary from light brown to bright red with H&E stain. It is common under ultrastructural examination to find more than one form of storage bodies in the same disease, and it is thus difficult to differentiate between different LSD. However, membranous cytoplasmic bodies

(i.e. membranous materials arranged concentrically) are most common in GM1 and GM2 gangliosidosis (Jolly & Walkley 1997), and in the present case, the lysosomal storage occurs as membranous swirls and vesicular profiles. Axonal swellings were prominent under light microscopic examination, and were shown to contain storage materials, and other structures which are referred to as tubulovesicular profiles, mitochondria, and dense bodies under EM. The ultrastructure of the axonal swellings in most types of neuronal storage diseases is observed to be remarkably similar, which may suggest that the defect in the lysosomal system subsequently leads to abnormal axoplasmic transport (Jolly & Walkley 1997).

In humans and probably in cats with LSD, there is an increased risk for secondary infections (Wood 1995), and this may explain the development of anterior uveitis and cystitis in this cat. Treatment of different LSD is still under investigation, and animal models have been used extensively for evaluating treatment for human storage diseases.

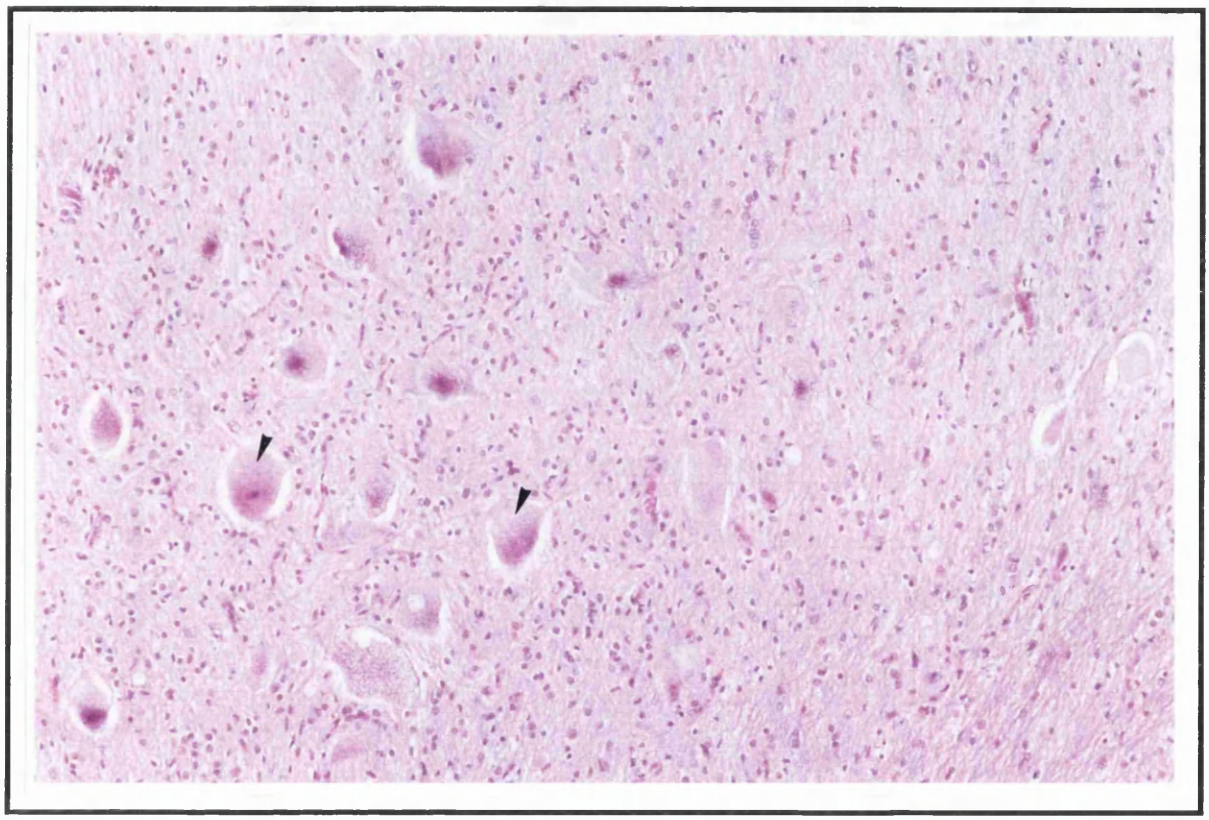

Figure 18.

Case 3. Deep cerebellar nuclei and white matter, showing accumulation of storage materials within neurones (arrow head). A generalised gliosis is present. (H&E, x 145)

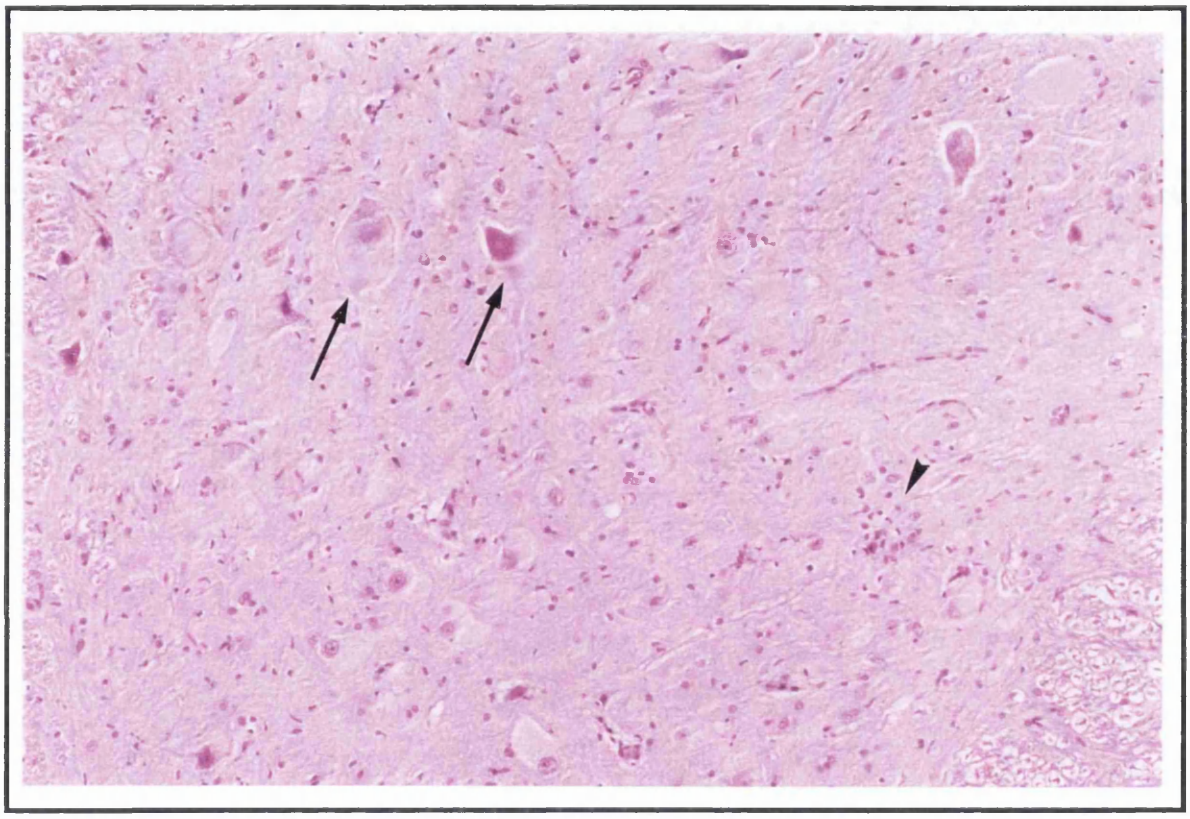

Figure 19.

Grey matter of spinal cord, showing neurones distended with storage material (arrow). Occasional microglial stars (arrow head) suggestive of neuronophagia are evident. (H&E, x 145)

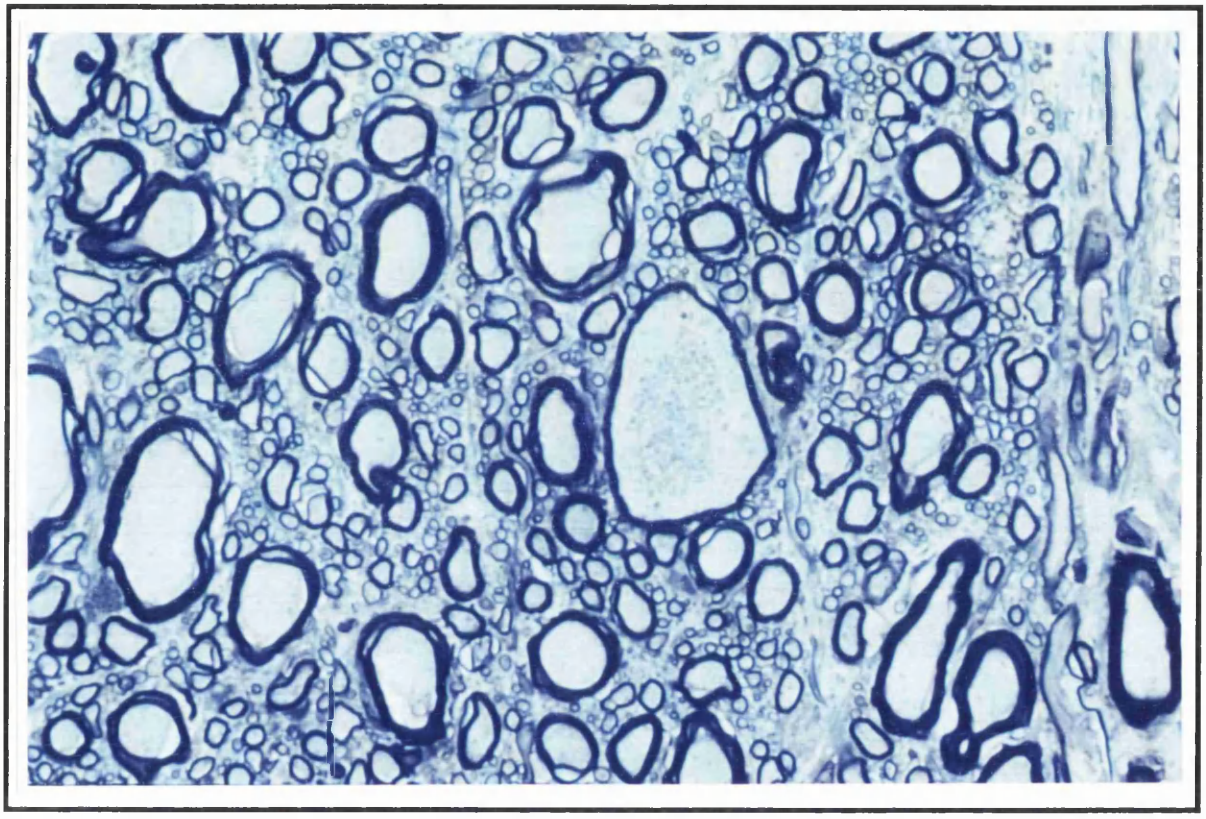

Figure 20.

White matter of ventral spinal cord showing a swollen axon containing organelles. (Resin-embedded section, stain with lead-citrate and uranyl acetate, x 1100)

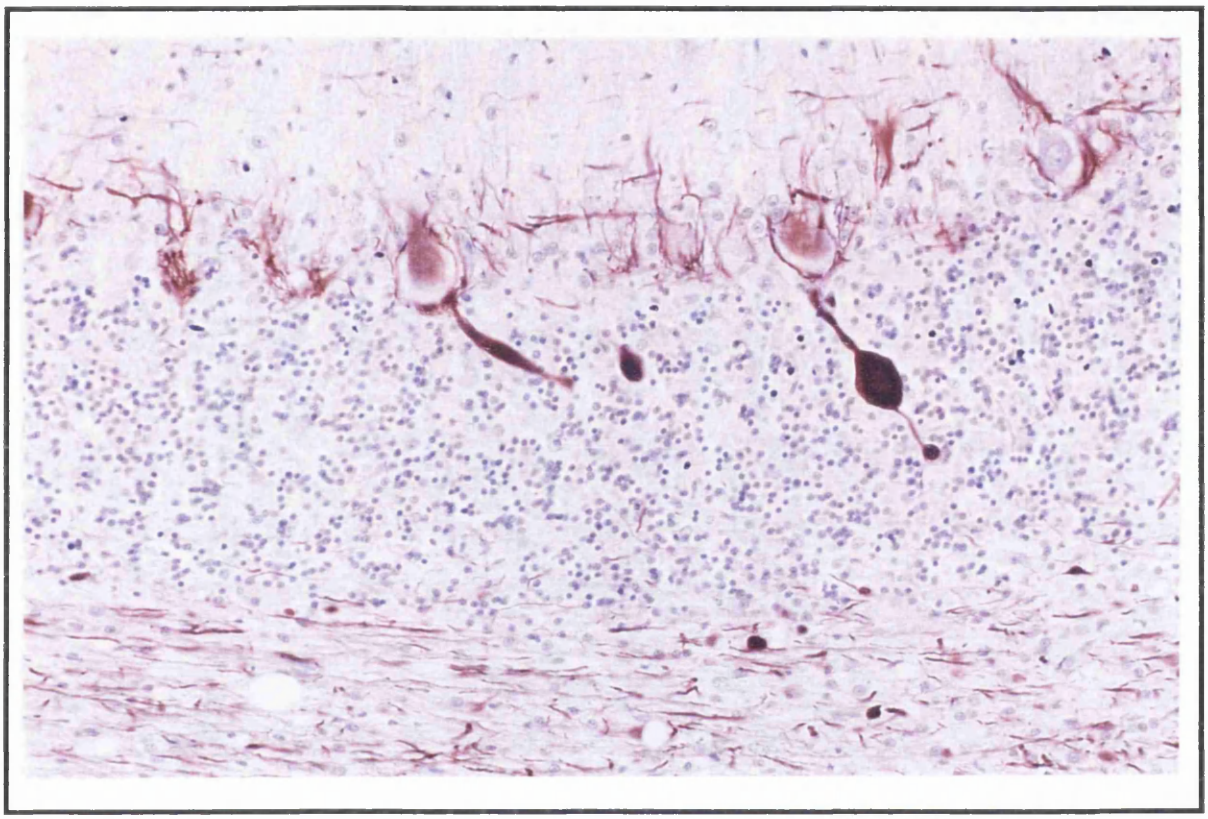

Figure 21.

Cerebellum, showing axonal swellings (torpedoes) in granule cell layer. (SMI-31, x 220)

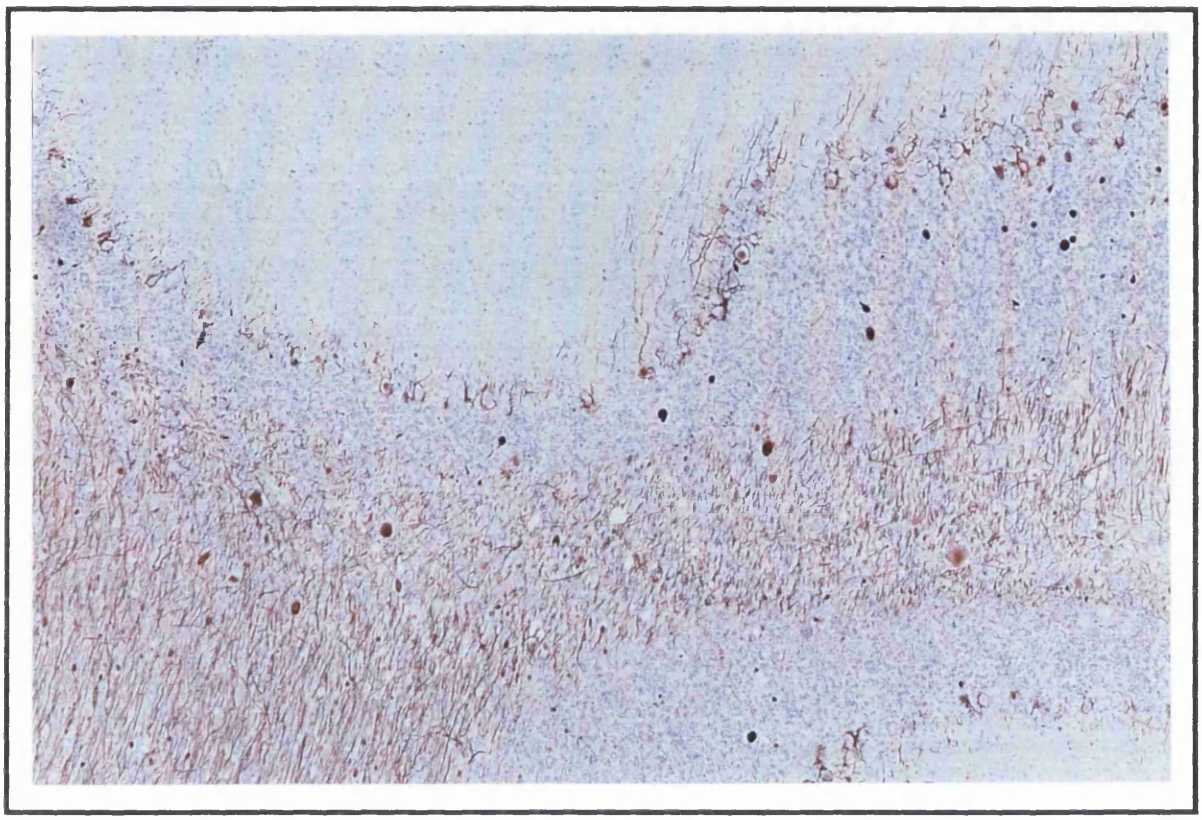

Figure 22.

Cerebellum, showing axonal swellings in granule cell layer and white matter. (SMI-31, x 60)

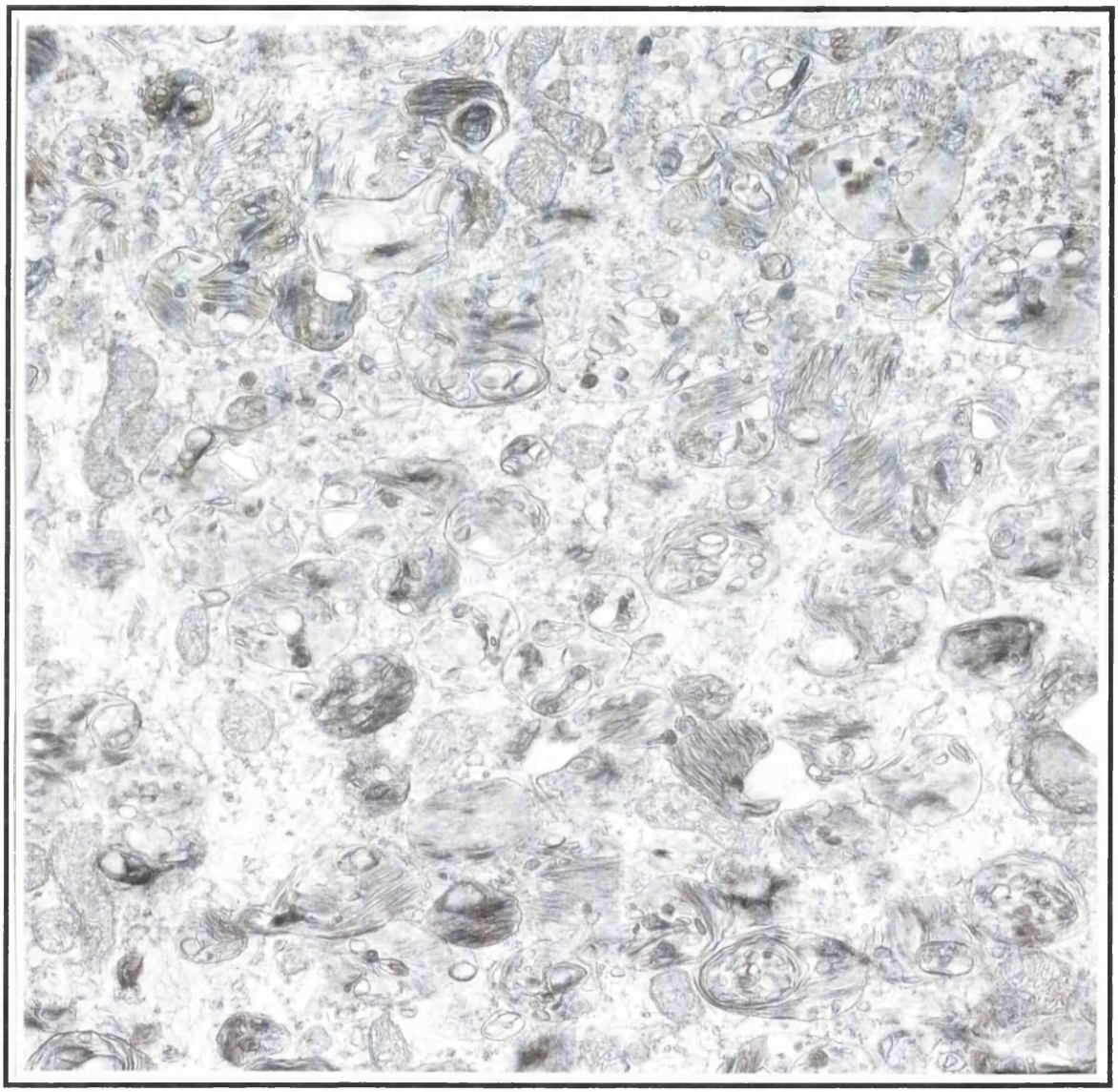

Figure 23.

Electron micrograph of neuronal cell body showing numerous multi-lamellar bodies. (x 10,000)

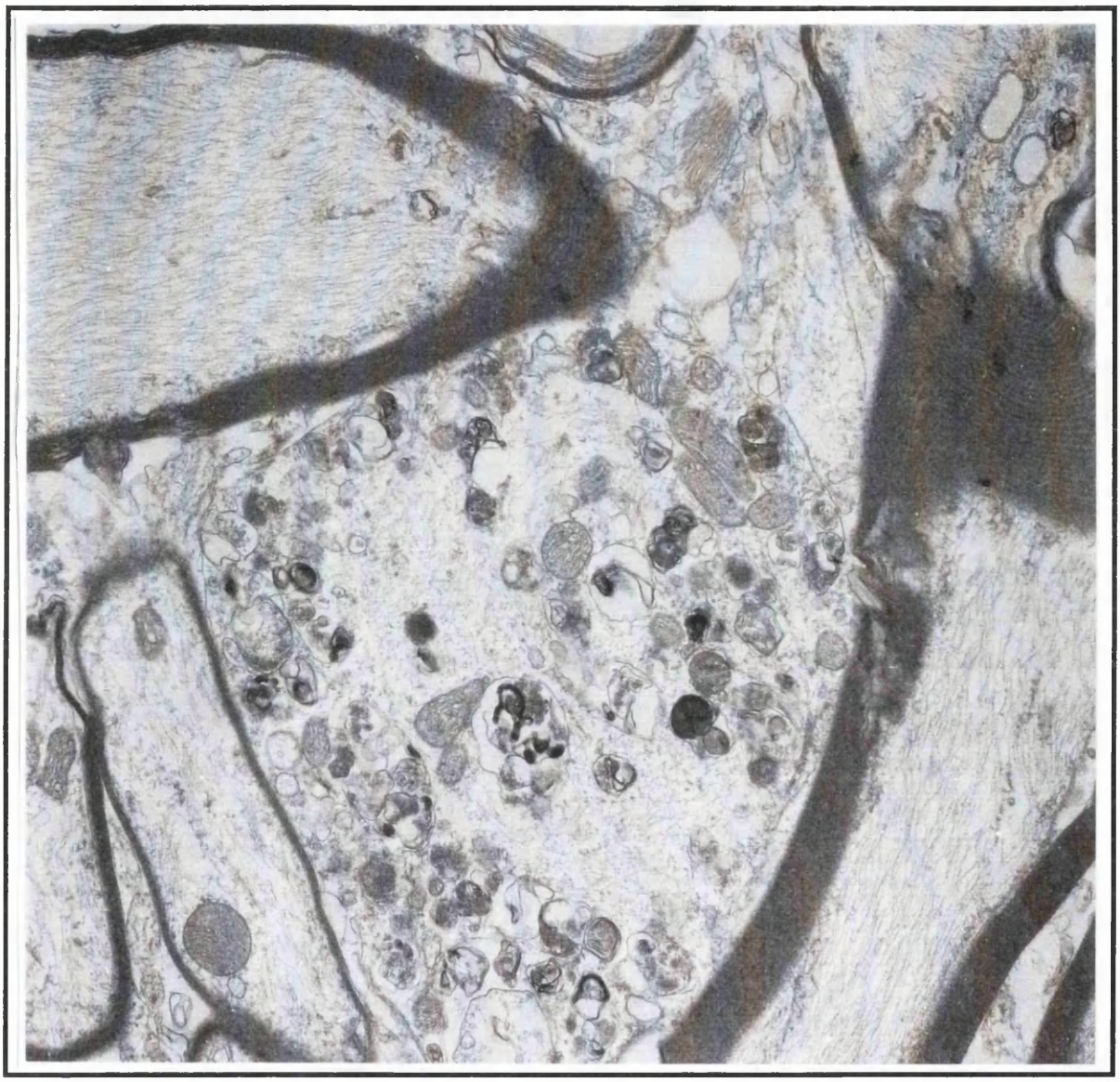

Figure 24.

Electron micrograph of axon to show numerous dense bodies and mitochondria. (x 7,500)

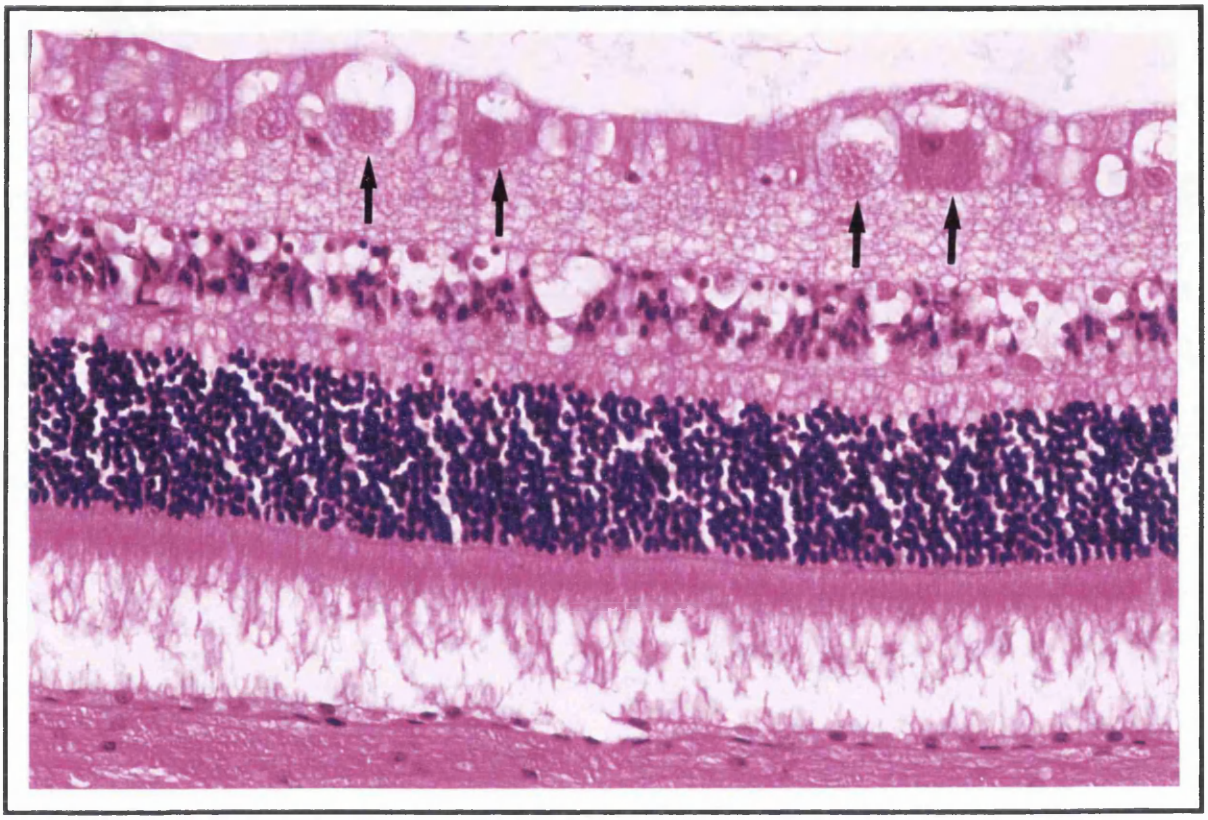

Figure 25.

Retina, showing retinal ganglion cells (arrow) distended with storage material. (H&E, x 700)

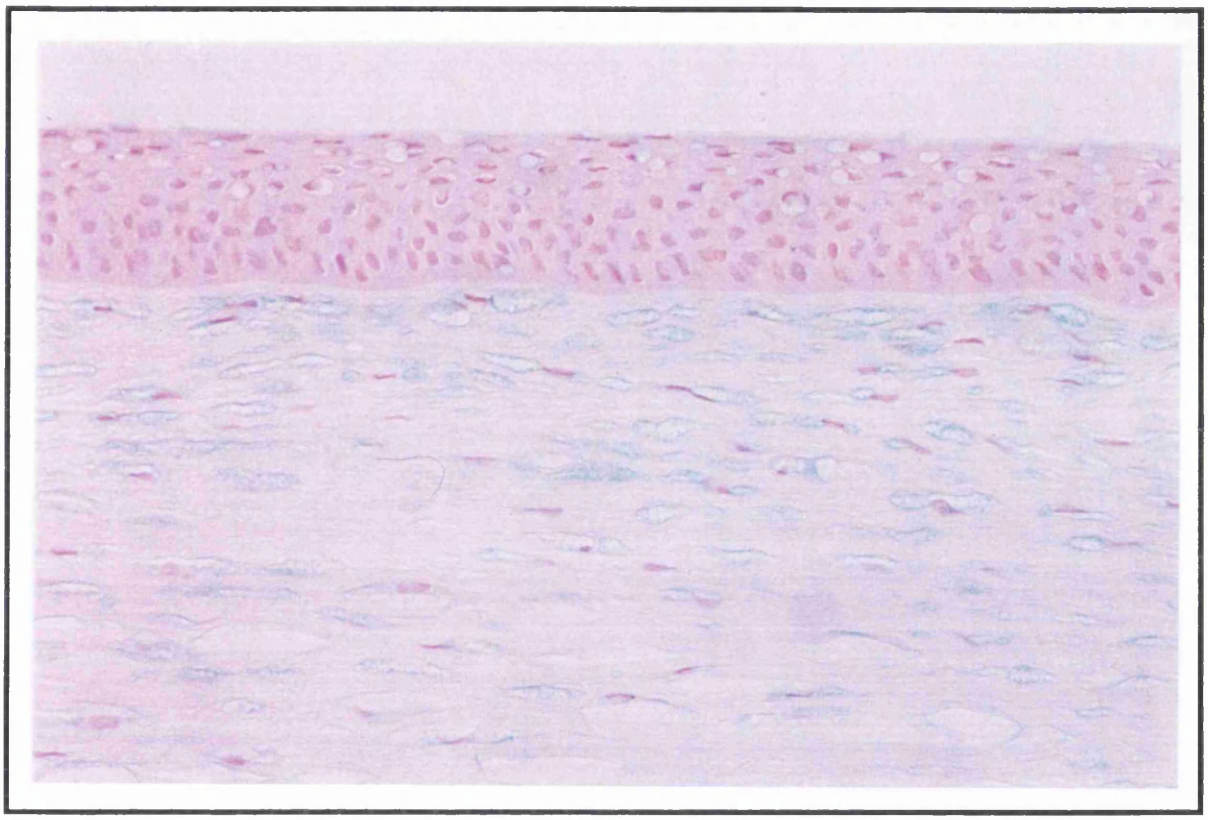

Figure 26.

Cornea, showing multiple intrastromal spaces stained positive either wholly or peripherally. (Alcian blue, x 220)

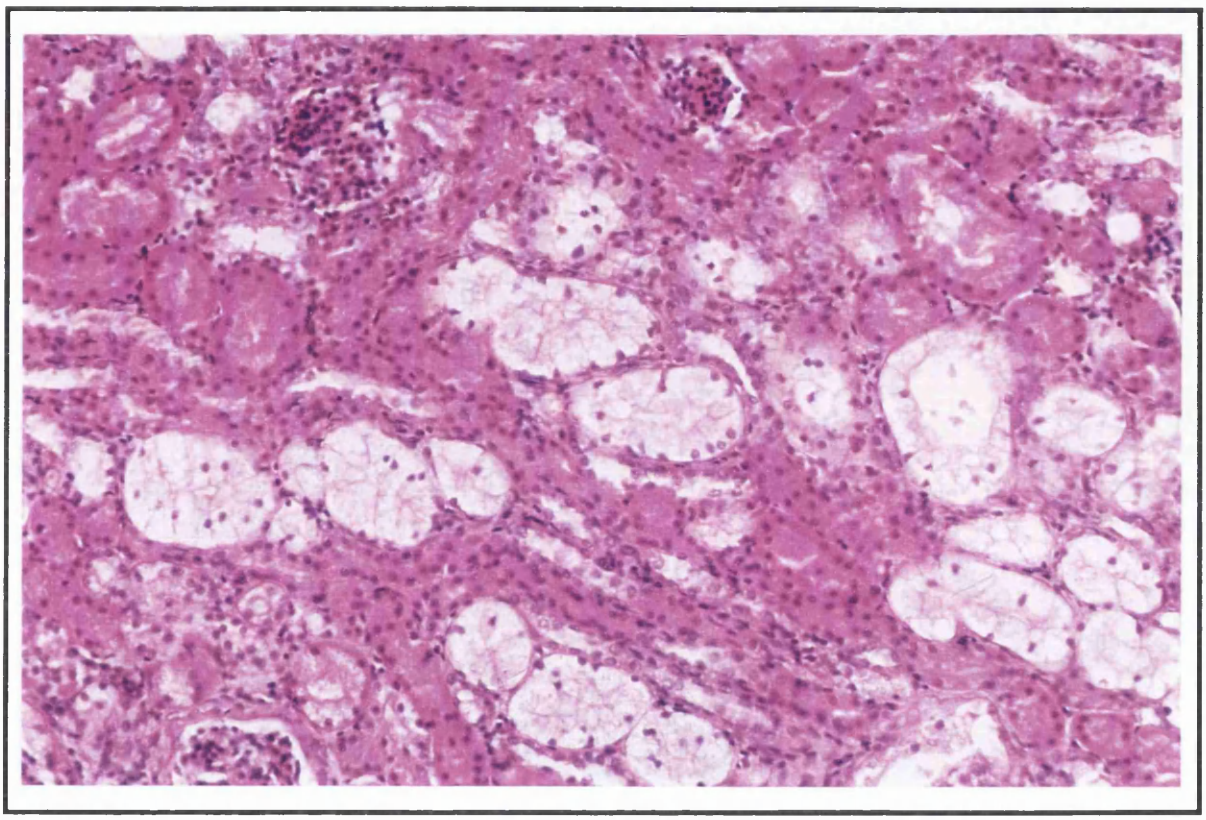

Figure 27.

Kidney, showing renal tubular cells distended with storage materials. (H&E, x 145)

2.2.2. DEVELOPMENTAL ANOMALY

The five cases (4 cats and 1 dog) reported in this section were thought to have a primary developmental anomaly of the cerebellum. A tentative diagnosis of cerebellar hypoplasia was made in the cats. One of these cases, is reported in detail and the details of the other cases are summarised. The suspected cerebellar anomaly in the dog is discussed separately from the cats.

Case 4: No. 130665

Signalment: Snoopy, 6.5 months old male Short-haired Colourpoint cat

This cat was presented to GUVH with a history of non-progressive shaking and uncoordinated movements since starting to ambulate. This cat was the only kitten born, although at pre-partum ultrasonography the queen had 3 kittens. There was a history of undefined illness during the queen's pregnancy, but she received no medication. The owner reported that the cat walked with a staggery gait, though he seemed normal while eating and could balance himself when playing with other cats. The cat could climb but had great difficulty in jumping up.

Clinical examination was unremarkable. The cat was alert, bright and responsive. Neurological examination revealed fine head and body tremor during rest, and an intention tremor when being manipulated or when movements were initiated. For example, when he tried to get into his basket, severe head bobbing was noticed. Posture and gait assessment demonstrated a crouched and wide-based stance of the hind limbs, hypermetria and truncal ataxia with preserved strength. Postural reaction showed brisk and hypermetric responses, and delayed onset and exaggerated response on hopping test. Menace response was present bilaterally. Fundoscopic examination revealed fine ocular tremor and peri-vascular hyper-reflectivity of the retina. The remaining cranial nerve examination was normal.

To ensure the disease was non-progressive, the cat was re-examined three months later. The owner reported that the cat could not jump up but managed to jump down. She also felt that the cat was slightly steadier and stronger than before, though he was still stunted. Neurological examination indicated a diffuse cerebellar disorder which had remained static compared to the last visit. Clinical and fundoscopic findings did not change compare to the previous examination. The owner was willing to keep the kitten as a pet.

The clinical findings were consistent with a diffuse cerebellar disease. Based on the age of onset (probably since birth), duration and probably non-progressive nature, a developmental anomaly most probably cerebellar hypoplasia was suspected.

Three other cats were included in this category. Signalment and history are reported and summerised in the following Table 6.

Table 6. Signalment and history

Case No.	Signalment	History
5 (132371)	1 year neutered male British Blue	Ataxia, poor balance, misjudging distance and height since the owner obtained him and his littermate (male) at 6 months old. There was a history of cat-flu. The clinical signs seemed to be worsened over the past few days and the gait seemed more exaggerated.
6 (132745)	5 month male Domestic Short-haired cat	Owners noticed stumbling and abnormal gait since they obtained him and his littermate (female) at 8 weeks old. Smaller than his littermate. Often misjudged height and had difficulty in assessing distance of close objects and bumped into them frequently. Occasionally lost balance and fell over. The owner felt that the cat was getting better, i.e. he could jump better.
7 (133500)	3.5 year neutered male Domestic Short-haired cat	Always had an abnormal gait, generalised and intention tremor since the owner got him and his littermate (male) at 8 weeks of age. Sudden onset of behaviour change and aggression towards the owners 3 weeks ago. The cat seemed to be scared of the owners and hiding away. The gait worsened and the cat could not get up onto bed and fell over more often. There was dramatic improvement after treatment with diazepam (Approved Prescription Services Ltd.).

Discussion

All four cats had a history of gait abnormality since the owners obtained them. Three owners had more than one cat and they recognised the gait abnormality by comparing the littermates. Only one case (Case 4) had a history of illness during the queen's pregnancy when possibly abortion occurred. The clinical signs were non-progressive for Cases 4 and 6, and had remained static until recently for Cases 5 and 7. A general systemic examination in all four cats were unremarkable. Neurological examination revealed a diffuse cerebellar problem. The cerebellar signs varied in severity, and the common clinical findings are recorded in Table 7.

Table 7. Clinical findings in the cats with suspected cerebellar hypoplasia.

Case No.	Ataxia	Generalised tremor H: head B: body	Intention tremor	Hypermetria	Wide-base stance	Falling over to either side	Hopping sense: delayed onset & exaggerated response	Absence of menace response	Fundoscopic examination	Progression of signs
4	++	++ (H, B)	++	++	++	++	++	–	Ocular tremor, peri-vascular hyper-reflectivity of retina	Lack of progression (3 month exam†)
5	+	+ (H)	–	+	+	++	–	–	Normal, no ocular tremor	Lack of progression (2 and 11 month phone‡)
6*	+	–	+	+	+	+	+	+	Normal, no ocular tremor	Lack of progression (2.5 month exam and 8 month phone)
7	+++	++ (H, B)	+++	+++	++	+++	+++	+	Obvious, fast, jerky ocular tremor	Lack of progression (2 month exam and 6 month phone)

Key: + presence, mild, difficult to detect or infrequent, ++ moderate, obvious or frequent, +++ severe, very marked or continuous

– absence

* Littermate of 132745 was examined and revealed normal neurological examination, including presence of menace response bilaterally.

† Exam: consultation and neurological examination performed.

‡ Phone: phone consultation only.

The most consistent abnormality reported by the owners was an abnormality of gait at the onset of ambulation. The clinical signs either remained static, or as in Cases 4 and 6, the owners thought that the cat was improving over time. Not all kittens in the same litters were affected. Common clinical findings included variable severity of ataxia, generalised tremor, intention tremor, hypermetria, wide-base stance, falling over, and delayed onset of postural reactions with exaggerated response. Lack of menace response bilaterally was present in 2 out of 4 cases. There was an obvious ocular oscillation (Case 7) or ocular tremor observed only on fundoscopic examination (Case 4) whereas 2 cats showed no ocular tremor (Cases 5 and 6). Cases 5 and 7 were presented as older animals with clinical signs (weakness and behaviour changes respectively) unrelated with the primary gait problem. Both cats recovered and the cerebellar signs returned to their previous level and remained static thereafter. In general, the cats in this series had non-progressive signs of cerebellar involvement, as shown by the lack of change at least one follow-up examination and additional telephone consultations.

In theory, animals born with developmental cerebellar anomaly have static signs. However, many owners may observe a slight improvement such as in Cases 4 and 6, this was probably due to accommodation through other senses such as vision and conscious proprioception (Kornegay 1991). Bilateral absence of menace response is a common finding, present in 2 out of 4 cases, however, this may not correlate to the degree of severity. Case 4 was more ataxic than Case 6, nevertheless, the former had a menace response while that in the latter cat was absent bilaterally.

Differential diagnoses for cerebellar signs in a young kitten include cerebellar hypoplasia, other forms of cerebellar malformation (i.e. cerebellar vermian hypoplasia or Dandy Walker syndrome), LSD, FIP, Toxoplasmosis, intoxications and trauma. LSD produce progressive signs, while FIP and Toxoplasma infection usually causes progressive multifocal nervous signs. Toxicities and trauma can be diagnosed from the history and physical examination. Signs of cerebellar hypoplasia are non-progressive and usually remain the same throughout the cat's life. In all four cases, a tentative diagnosis of cerebellar hypoplasia possibly due to *in utero* or perinatal FPV infection was made, based on the non-progressive nature (over several months) of pure cerebellar signs. CSF analysis from confirmed cases of feline cerebellar hypoplasia is normal (Rand *et al.* 1994 b).

Thus, a definitive diagnosis of panleukopaenic virus-associated cerebellar hypoplasia can only be made by:

1) Isolation of the panleukopaenia virus from the cerebellum or other organs (Csiza *et al.* 1971 b), and/or identification of serum antibodies to panleukopaenia virus (Csiza *et al.* 1971 b);

2) Sagittal MRI of the brain (Thomson *et al.* 1993); and

3) Histopathological examination of the cerebellum.

In the majority of cases, the owners usually did not pursue further investigation due to the static signs, and general good health of the cats. They would rather wait and see if the signs remain non-progressive over several months. Thus a tentative diagnosis of cerebellar hypoplasia due to FPV infection, was made based on the non-progressive nature of cerebellar signs, as in all four cases presented here.

Case 8: No. 132383

Signalment: Trixie, 1 year old female Jack Russell Terrier cross

This dog was presented to the GUVH with a history of hind limb and truncal ataxia, since the owners acquired the dog at 8 months of age. She was the smallest among her littermates and the other 3 pups were apparently normal. She was fully vaccinated and had always been healthy. The owner thought that the dog had an abnormal gait since a puppy but they regarded it as merely "puppy behaviour". When the dog was running, her hind limbs caught up with the fore limbs and the clinical signs were exacerbated by excitement. When Trixie was younger, she would occasionally bump her nose into the food. In general, the owners did not feel that the condition was progressive, but could not be entirely sure.

A general physical examination was unremarkable. The dog was bright, alert and responsive. Observation revealed generalised cerebellar ataxia, truncal sway, head and neck sway, and intention tremor. The gait was characterised by marked spasticity, and could be described as "dancing" or "prancing". All four limbs were hypermetric although the hind limbs were more severely affected. Whilst walking down stairs, the hind limbs were lifted so high that the dog often lost balance and fell over.

Neurological examination revealed normal conscious proprioception. Reflex stepping and hip sway tests were markedly reduced. Hopping sense was relatively normal in the fore limbs but showed a slow onset and exaggerated response in the hind limbs. Cranial nerve examination was normal. Menace response was present bilaterally.

Clinical findings revealed a diffuse cerebellar problem. The lesion was most likely to be in the cerebellum, and might also involve the spinocerebellar tracts in the spinal cord. In view of the good physical condition of the dog, we decided to see whether there was any progression over time, and no further investigations were performed at this stage. The clinical signs were video-taped. The dog was reassessed 3 and 7 months later. The owner reported no progression of the clinical signs and neurological examination revealed no change of neurological status, by comparing with the previous video recording.

Discussion

In this case, no ancillary investigations were performed at the time of presentation. A "wait and see" protocol is indicated in this case in view of the good body condition of the dog. Congenital cerebellar anomaly is very likely if the signs remain static, however, if the clinical signs progress over time, degenerative cerebellar disease is more likely. Cerebellar anomaly in dogs,

is usually not caused by *in utero* viral infection, in contrast to cats where FPV infection accounts for the majority of static cerebellar dysfunction. Puppies surviving CHV infection may develop a residual cerebellar ataxia which is non-progressive (Percy *et al.* 1971). However, there was no history of illness before the owners acquired the dog. The other 3 littermates are normal which makes CHV infection less likely, because usually the whole litter is affected and occasionally only one puppy can survive the systemic infection.

Cerebellar hypoplasia in dogs may be inherited because no infectious causes have been found (Kornegay 1990 b). An autosomal recessive mode of genetic transmission was hypothesised from a study of the family history of the Chow Chows with cerebellar hypoplasia (Knecht *et al.* 1979). In the St Bernard dogs with cerebellar cortical dysplasia, the Irish Setters and the Wirehaired Fox Terriers with cerebellar dysplasia and cerebral lissencephaly, a heritable basis was suspected but not proven (de Lahunta 1980 a, Franklin *et al.* 1997). Other forms of canine cerebellar malformation have been described in the literature (See section 1.6.3.1), again, there is no proof of inheritance. However, in the report of Harari *et al.* (1983), the presence of inflammatory lesions in the brain support the hypothesis of an in utero viral infection, causing cerebellar agenesis in two Siberian Husky littermates. MRI may be helpful in identifying congenital cerebellar anomalies (Thomson *et al.* 1993).

In Jack Russell Terriers, an inherited cerebellar ataxia primarily associated with degenerative myelopathy has been described in UK (Hartley & Palmer 1973), in which the clinical signs resemble a cerebellar disorder but the microscopic lesions were not reflected in the cerebellum. The pathology was characterised by focal symmetrical demyelination of the dorsolateral and ventromedial columns of the spinal cord, and was most evident in the spinocerebellar tracts in the cervical segments. Widespread Wallerian degeneration was evident in the brain particularly the central auditory pathway and the spinal cord. These animals usually have a progressive course of disease, which is not consistent with the case described here.

2.2.3. CEREBELLAR NEOPLASIA

Two cases were presented to the GUVS with an initial diagnosis of paradoxical vestibular syndrome, however, only one was very suspicious of cerebellar neoplasia, and this is discussed in detail.

Case 9: No. 133247

Signalment : Chester, 6.5 year old male English Springer Spaniel, BW 27 kg

This dog was presented with a history of gradual onset of inco-ordination over 3 months. The owners noticed several "strange" episodes, during which the dog staggered and lay down, and appeared to be extremely tired. The dog did not lose consciousness and recovered within 5 minutes. The owners had noticed a rapid progression in the past 2 to 3 weeks regarding poor balance and inco-ordination. In addition, jerky head movements were observed. The dog had difficulty in turning, and tripped when going upstairs, dragged its right front paw and nails while walking. The right hind leg crossed under the body and the dog walked diagonally to the left rather than in a straight line. These signs were exacerbated by excitement. The owners did not think that the dog was in pain or discomfort, although the dog seemed to be "confused", not knowing what was going on.

Examination revealed ataxia and right-sided hypermetria, with the hind leg more affected than the fore limb. During walking, the dog leaned and drifted to the left and also fell to the left. Shaking the body led to loss of balance and falling over. He had great difficulty in going down stairs and frequently fell over.

Neurological examination revealed normal conscious proprioception. Reflex-stepping was normal. The dog showed markedly slow onset and exaggerated response on hopping of the right limbs, and hemiwalking on the right side showed similar response. The left limbs responded normally to the hopping and hemiwalking tests. Cranial nerve examination was normal.

Clinical findings were suggestive of paradoxical vestibular syndrome: ipsilateral cerebellar signs and contralateral vestibular signs. Localisation of the lesion was assigned to the right flocculonodular lobe of the cerebellum, cerebellar medulla or the caudal cerebellar peduncle. A mass lesion such as neoplasia or focal form of GME was suspected.

Routine haematology and biochemistry were unremarkable. A CSF sample collected from the cisterna magna revealed a normal cell count (3 WBC/mm^3) and protein level (80 mg/l). Chest radiographs were not taken.

The dog was discharged on Betsolan® (Bethamethasone, Mallinckrodt Vet Ltd.) 0.5 mg q6h for 2 days, then 0.25 mg q6h for 2 days, then reduced to q12h and q24h, each for 2 days. However, the dog did not respond to treatment, and deteriorated rapidly. The owner reported that the dog appeared to be more unsteady, extremely tired and did not want to get out of bed. Due to the rapid progression and a very poor prognosis, they elected for euthanasia. A necropsy was not performed.

Discussion

The case is a typical presentation of paradoxical vestibular syndrome, and a tentative diagnosis of cerebellar neoplasia was made, based on progressive signs and lack of response to treatment. A focal form of GME or abscess in the cerebellum may present similarly, however, inflammatory diseases usually exhibit CSF changes, in particular, pleiocytosis (Adamo & Clinkscales 1991). However, a definite diagnosis could not be made. Imaging such as CT or MRI would have been useful to reach a diagnosis. Biopsy of the mass may provide the definite diagnosis.

Analysis of CSF was normal in this case which indicated the lesion was probably deep in the cerebellum, thus there was no connection with the CSF pathway. The CSF associated with brain neoplasia in dogs is often described as albuminocytological dissociation, which is an increased protein level in the presence of a normal or slightly raised total WBC count (cited in Bailey & Higgins 1986 a, Adamo & Clinkscales 1991). This is, however, not universal, because the characteristics of the CSF depend on the location and the biological behaviour of the neoplasm. If the tumours are close to the ventricular surface, or necrotic areas are present, or when the tumours infiltrate the leptomeninges, then the WBC count and protein level in CSF will be increased (cited in Bailey & Higgins 1986 a). Normal CSF is encountered most often with deeply seated parenchymal tumours such as astrocytomas and oligodendrogliomas (Bailey & Higgins 1986 a). Neoplasms producing paradoxical vestibular syndrome may yield different CSF results. In two cases of cerebellar meningioma (Adamo & Clinkscales 1991, Quesnel & Parent 1995) and malignant cerebellar astrocytoma (Panciera *et al.* 1987), the CSF showed albuminocytologic dissociation. Schulman *et al.* (1992) reported multiple meningioma in a dog with paradoxical signs which had pleiocytosis and raised protein level in the CSF. However, in three cases of choroid plexus tumours (Skerritt & Whitbread 1985, Chénier *et al.* 1983) causing

paradoxical vestibular syndrome, the CSF analysis was normal. In other cerebellar tumours producing paradoxical signs, CSF analysis was not performed (Smith & Honhold 1988, Muñana 1991).

CSF collection in animals with paradoxical vestibular signs is at a higher risk of inducing brain herniation due to raised intracranial pressure by the mass. Instead, CT or MRI is preferred if clinical signs of raised intracranial pressure are present, i.e. depression, disorientation progressing to stupor or coma. Although these signs were absent in the present case during the initial clinical examination, brain herniation was still possible and thus precautions had been taken during anaesthesia, such as using isoflurane instead of halothane, pre-oxygenation, and positive ventilation. These procedures are thought to reduce $PaCO_2$ and intracranial pressure.

2.2.4. INFECTIOUS CEREBELLAR DISEASES

2.2.4.1 FIP

Two cats were presented to the Neurology service of GUVS due to systemic signs and cerebellar ataxia. A diagnosis of non-effusive form of FIP infection was made, based on serology. The first case is reported in detail and a comparison of the signalment, history, clinical findings, laboratory results of the two cases is made and summarised in Table 8.

Case 10: No. 131616

Signalment : Ginger, 8.4 months old Domestic short-haired cat, BW 2.13 kg

This cat was presented with a history of dullness, anorexia, weight loss, gingivitis and progressive imbalance (swaying of the back) for two months, which seemed to respond to antibiotics initially but relapsed. Clinical examination revealed poor body condition including underweight and stunted growth, marked depression and mild head bobbing. He developed a wide-based stance in his hind limbs and truncal sway while standing. There was no obvious hypermetria. Conscious proprioception was present, however, the reflex stepping and hip swaying tests were slow. The cat was weak in all limbs on hopping. Cranial nerve examination revealed reduced menace response bilaterally. Ophthalmologic and fundoscopic examination did not reveal any signs of ocular disease. The clinical findings were suggestive of a diffuse CNS disease.

Haematology was normal, and biochemistry revealed mild elevation in urea (10.6 mmol/l), albumin (40 g/l), and globulin (38 g/l). FCoV antibody titre was 1: 1280, and titres to FIV antibodies and FeLV antigen were negative. Analysis of cervical cisterna CSF revealed moderate pleiocytosis (57 WBC/mm^3). Cytological examination revealed 53% lymphocytes, 27% macrophages, 15% reactive plasmacytoid cells, 4% neutrophils, and the remainder plasma cells. CSF protein was markedly elevated at > 2 g/l. A diagnosis of FIP (dry form) was made, based on the history, clinical and laboratory findings.

A series of neurological examinations were carried out to monitor the progress of the disease. The cat deteriorated rapidly over several days. Re-assessment revealed pronounced depression. When in sternal recumbency, the cat held his head in a left lateral deviated direction, close to the flank. Head tremor and intention tremor were more obvious. While he was standing, moderate head and truncal ataxia were noticed, and he developed a wide-based stance in both fore and hind limbs. He was moderately ataxic, falling frequently to either side, and dragged

his forelimbs. A more exaggerated gait was noticed on the left side of body. Paw position sense was absent in the left forelimb. Visual and tactile placing responses were absent in the fore limbs, with intact tactile placing responses in the hind limbs. Hopping was slow to absent in the left fore. Increased muscle tone and patellar reflexes were noted.

A week after admission, the cat was inappetant, and remained in sternal recumbency. He developed tachypnoeia with marked abdominal movement. He showed tetraparesis with marked truncal, head and neck ataxia, wide-based stance, and a hypermetric hind limb gait. Postural responses were absent (Figure 28) and the withdrawal reflex was slow in onset in all limbs. Reduced menace response and sluggish oculocephalic reflex were also apparent. Due to the grave prognosis, the cat was euthanased and a full post-mortem examination was performed.

Table 8. Comparison of the two cases of CNS form of FIP

	Case 10 (131616)	Case 11 (132764)
Signalment	8 month male DSH	9 year neutered female DSH (BW 2.8 kg)
History	Dullness, anorexia, weight loss, gingivitis, progressive imbalance for 2 months	3 months wax & wane ocular problem (discharge & redness), oculonasal discharge & sneezing for 2 weeks, unresponsive to antibiotics.
Clinical findings	Systemically ill & multifocal CNS signs (including cerebellar signs)	Respiratory signs: increased inspiratory noise, serous nasal discharge Ocular signs: anterior uveitis with aqueous flare, corneal oedema, keratic precipitates
Haematology	Normal	Non-regenerative anaemia, increased rouleaux RBC formation, mature neutrophilia, lymphopaenia, reactive lymphocytes & neutrophils with Dohle bodies
Biochemistry	↑urea, albumin, globulin, normal albumin to globulin ratio (A:G 1.05)	↑urea (15.8 mmol/l), creatinine (211 umol/l), protein (112 g/l), globulin (87 g/l), A:G 0.29, normal T_4. Serum protein electrophoresis: polyclonal gammalopathy.
Serology	FCoV antibody 1:1280 FIV antibody, FeLV antigen negative	FCoV antibody >1280 FIV antibody, FeLV antigen negative
CSF	Mononuclear pleiocytosis, marked elevation of protein > 2 g/l	Not evaluated
Treatment & response	Prednisolone, non-responsive to treatment & deteriorated rapidly.	Respond on combined oral antibiotic, prednisolone & topical steroid therapy for a month but relapsed 6 weeks later with sudden onset diffuse cerebellar signs (ataxia, hypermetria, intention tremor). Failed to respond to high dose of prednisolone, deteriorated rapidly over a few days & became non-ambulatory. Proprioceptive deficits in all four limbs.
Histopathology	Confirm FIP, see text	Not evaluated

Pathology

Gross examination revealed a small pyogranuloma on one pole of the left kidney. The cerebral blood vessels appeared congested (Figure 29) and there was a degree of hydrocephalus.

Sagittal brain sections and transverse sections of the spinal cord were available for histopathological examination. The pathology were dominated by an intense cellular infiltration predominantly in the periventricular region of all ventricles (Figure 30 a & b) and the central canal of the spinal cord (Figure 31). In regions more remote from the ventricular system, infiltration was minimal or absent. In the affected areas, the infiltration was both perivascular and interstitial. Perivascular cuffs can be comprised of multiple layers of cells. The cells were predominantly mononuclear, containing a large number of plasma cells, and some lymphocytes (Figure 32). In some regions, necrosis of tissue had occurred. Blood vessels were markedly congested, and haemorrhage was present within the tissue.

Within the cerebellum, in addition to the inflammatory changes described above, there was some infiltration in the deep cerebellar white matter and occasional degenerating fibres (Figure 33). The majority of the cerebellar cortex appeared intact in most lobes. However, in lobes associated with intense inflammatory reaction, necrosis of cerebellar tissue was evident (Figure 34).

Discussion

The most consistent abnormalities in these two cases were a chronic history of systemic illness and serological detection of FCoV antibody titre either equal to or greater than 1280. Systemic involvement is common in FIP (dry form), in addition to neurologic and ocular disease. However, in a study reported by Kornegay (1978), some cats were presented with only neurologic dysfunction with or without ocular involvement. In the literature, the common systemic signs include depression, anorexia, weight loss, pyrexia, upper respiratory infection, and ocular disease such as iritis, anterior uveitis and keratitis (Kornegay 1978, Kline *et al.* 1994, Rand *et al.* 1994 a). Both cases in this study were presented with many of the signs described.

The most frequently neurologic signs reported in the literature included depression, ataxia, head tremor, nystagmus, seizures, and paraparesis (Kornegay, 1978, Kline *et al.* 1994, Rand *et al.* 1994 a). The CNS signs appear to be multifocal in nature at the end stage although a predominant cerebellar involvement may be seen initially. The cerebellar signs may develop early with an insidious onset (Case 10, 2 months before euthanasia) or acutely in the later stage

(Case 11, several days). The cerebellar signs are usually typical, although very rarely, decerebellate posture is seen (opisthotonus, forelimb extension, hind limb flexion) (Kline *et al.* 1994). In general, the development of CNS signs usually indicates an end-stage disease, as both cats in this study deteriorated rapidly and had to be euthanased upon humane grounds. This can be used as an prognostic indicator.

Although all cats are susceptible to FIP, the disease is primarily seen in cats between 3 months and 3 years of age (McReynolds & Macy 1997). Another peak in disease incidence occurs in cats older than 10 years, which is thought to be due to an age-associated decline in immune response (Kass & Dent 1995). The two cases in this study correspond to the two conditions respectively.

Clinical pathology of Case 10 was not consistent with FIP infection compared with the typical presentation of Case 11, i.e. hyperproteinaemia with hyperglobulinaemia, an albumin to globulin ratio less than 0.6, non-regenerative anaemia and characteristic cytological findings. Thus a diagnosis of FIP could not be based on routine haematology and biochemistry. It is known that no single indicator of FIP (e.g. coronavirus serology, complete blood count, biochemistry, PCR) is sufficiently reliable to confirm an antemortem diagnosis of FIP, however, a combination of these indicators is highly suggestive of FIP (McReynolds & Macy 1997).

CSF analysis of Case 10 demonstrated characteristic abnormalities including marked pleiocytosis, elevation of protein level more than 2 g/l, and cytologic changes, which were highly suggestive of FIP infection. The total protein can range from 0.56-6.6 g/l (Kornegay 1991, Kline *et al.* 1994, Rand *et al.* 1994 a). The CSF total white cell count is usually increased, and can be as high as 2500 cells/mm^3 (Rand *et al.* 1994 a). A mixed population of neutrophils, lymphocytes, and macrophages may be seen, though neutrophils may be the predominant cell type in the CSF cytology and can range from 4-98 % (Kornegay 1978, 1991, Kline *et al.* 1994, Rand *et al.* 1994 a). In Case 10, CSF analysis provided a more accurate diagnosis of FIP than routine haematology and biochemistry parameters. CSF feline coronavirus titre and PCR may be diagnostic. In addition, the finding of hydrocephalus on a CT scan in cats with signs associated with FIP support a diagnosis as the majority of cats with neurologic form of FIP have some degree of hydrocephalus in one or more ventricles (Kline *et al.* 1994).

Histopathological examination of Case 10 confirmed a diagnosis of FIP and correlated very well with the clinical presentation. The severe pyogranulomatous inflammation of the meninges, choroid plexus, ependyma and brain parenchyma is the cause of the multifocal CNS

signs. The inflammatory reaction and the tissue necrosis associated within the cerebellum was the cause of cerebellar signs in this cat. The nature of the hydrocephalus is obstructive, due to the inflammatory ependymal lesions which lead to accumulation of inflammatory cells at narrowing sites of the CSF pathway (i.e. mesencephalic aqueduct, lateral apertures, and arachnoid villi) (Kline *et al.* 1994). Normal CSF flow to the subarachnoid space is thus prevented, causing ventricular dilation rostral to it. The same lesion occurring in the central canal or raised intraventricular pressure can lead to hydromyelia at all levels of the spinal cord (Summers *et al.* 1995).

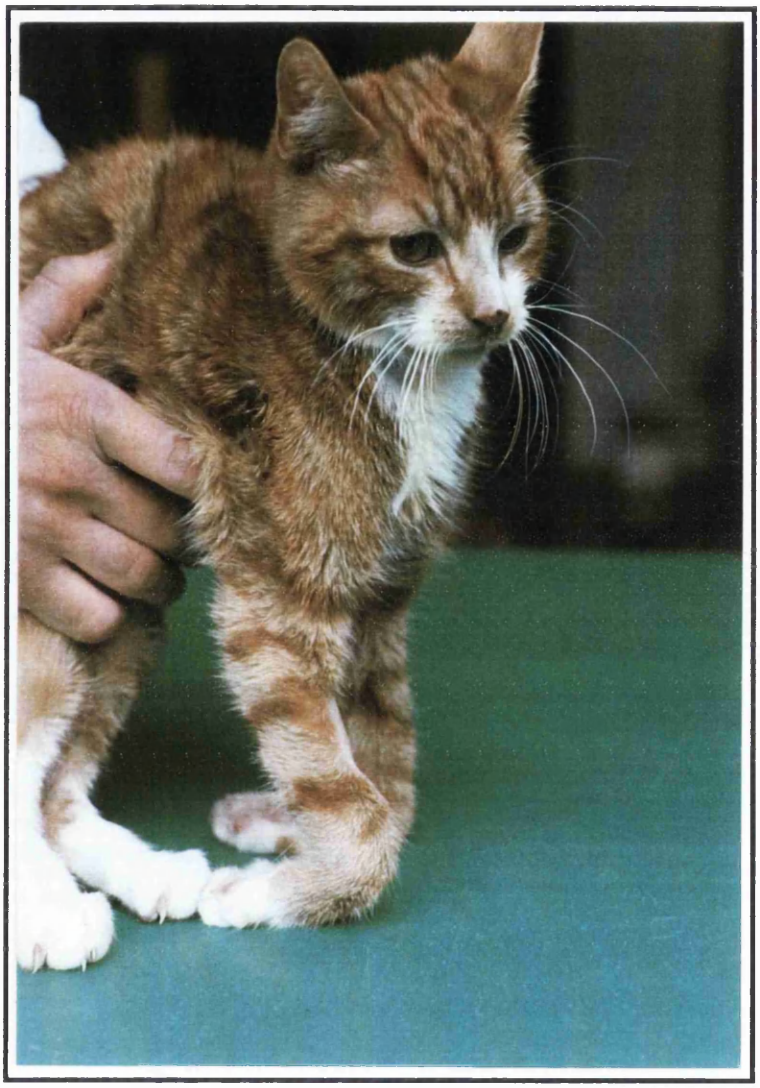

Figure 28.

Case 10. Cat showing absence of paw positioning.

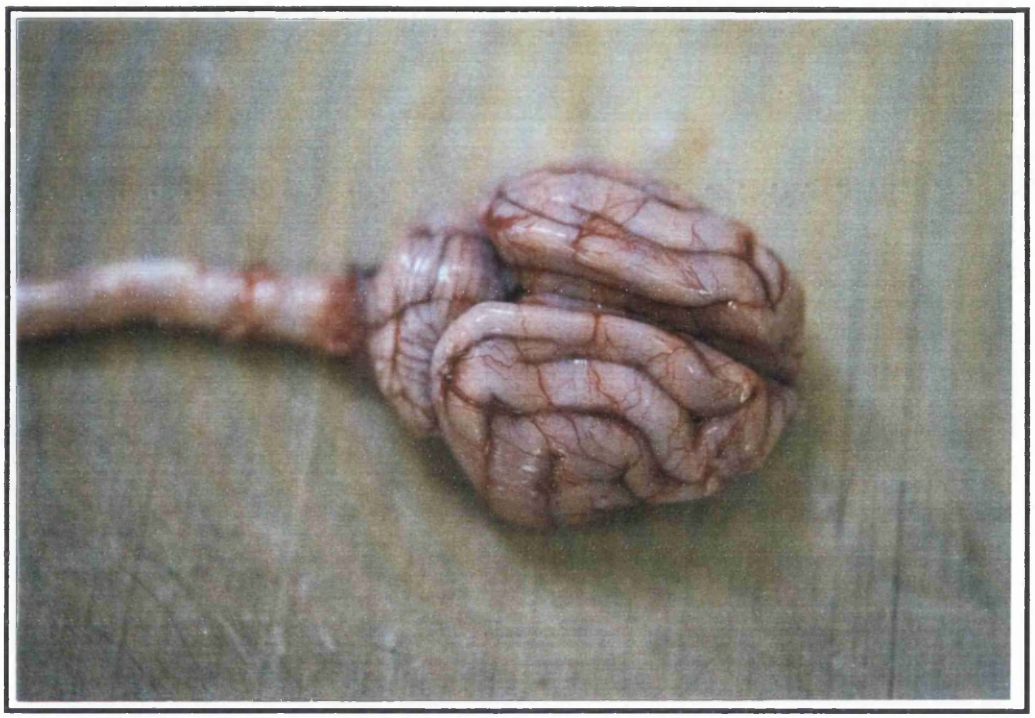

Figure 29.

Gross pathology. Congestion of cerebral blood vessels.

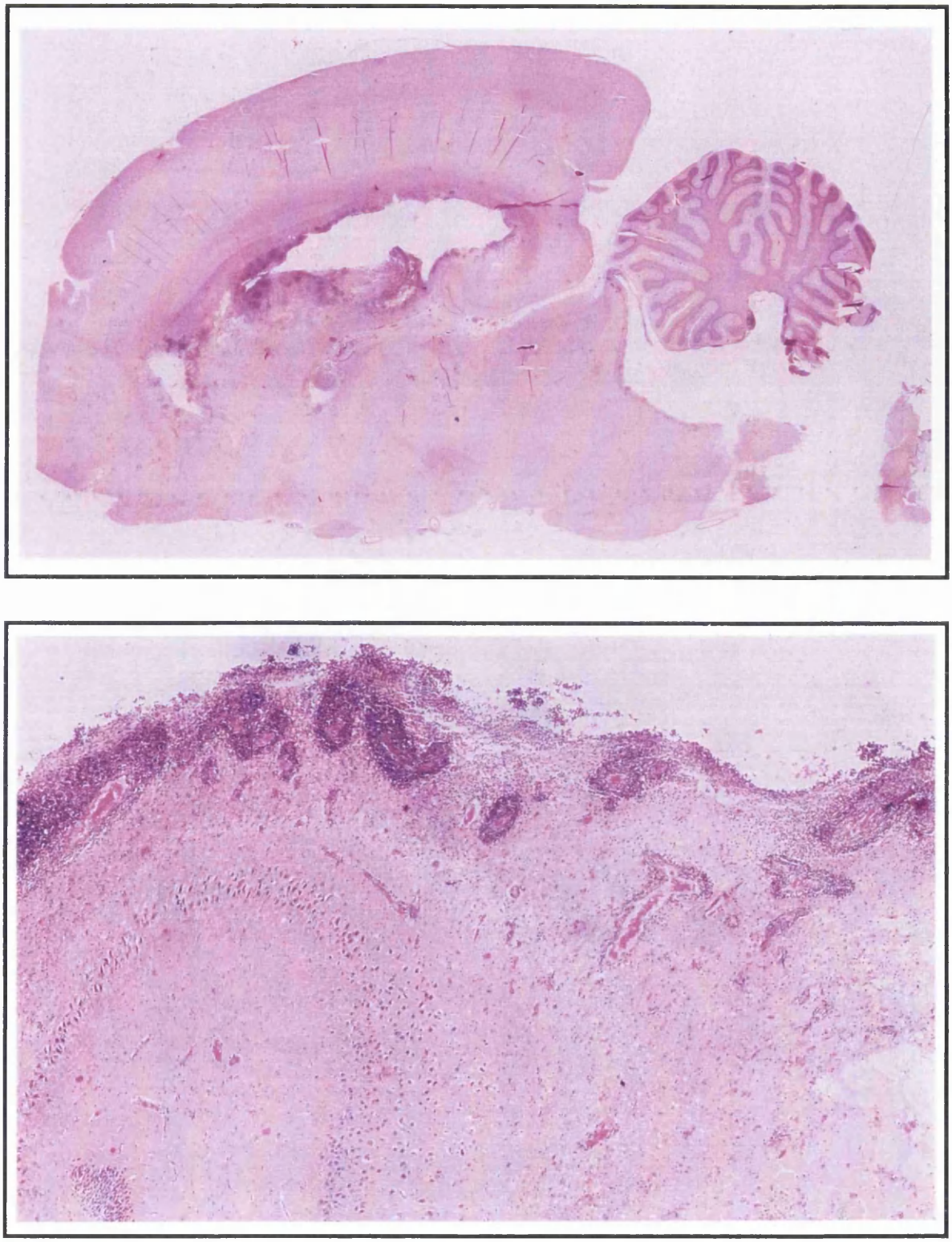

Figure 30.

A. Longitudinal section of brain, showing intense cellular infiltration inperiventricular region of the lateral ventricle. (H&E, x 3)

B. The hippocampus region from Figure 30 A, showing severe cellular infiltrate and perivascular cuffs. (H&E, x 44)

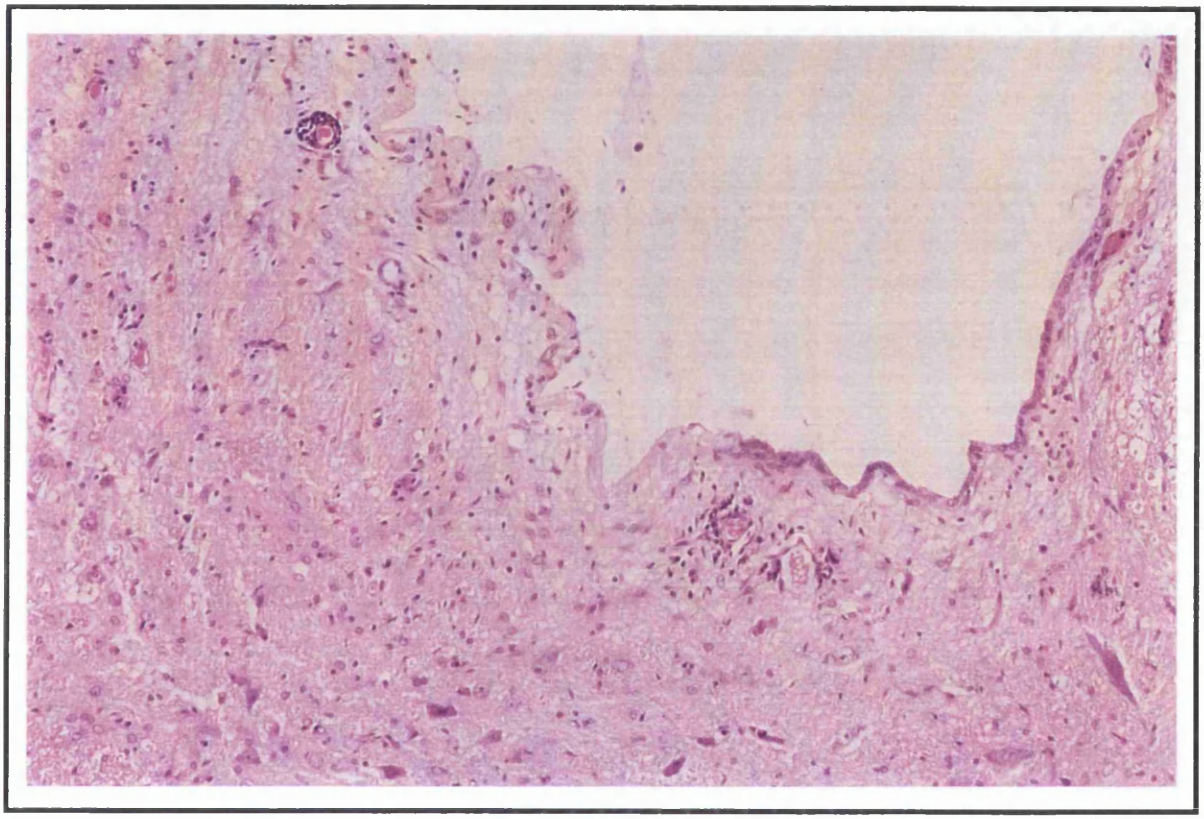

Figure 31.

Spinal cord adjacent to a distended central canal to show mild perivascular cuffs and gliosis. (H&E, x 145)

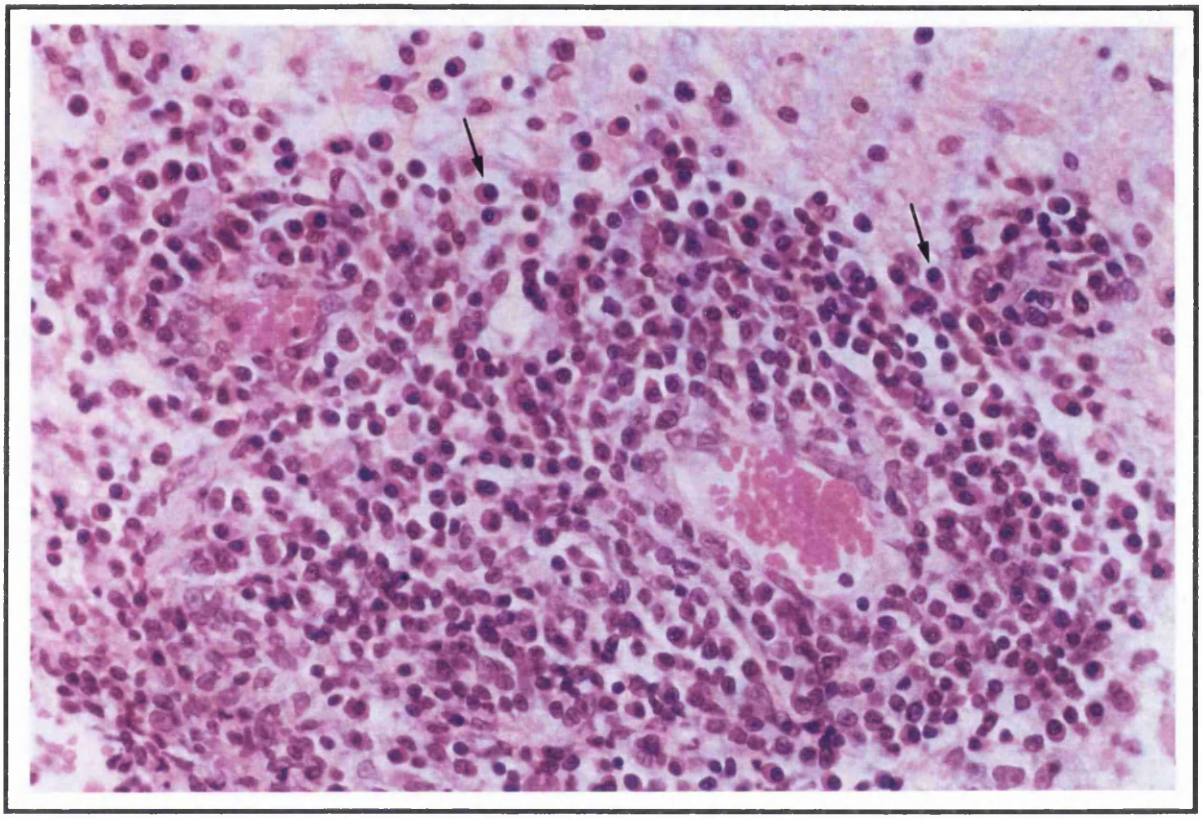

Figure 32.

Higher power view of the perivascular infiltrate which is composed mainly of mononuclear cell. Plasma cells (arrow) are particularly prominent. (H&E, x 440)

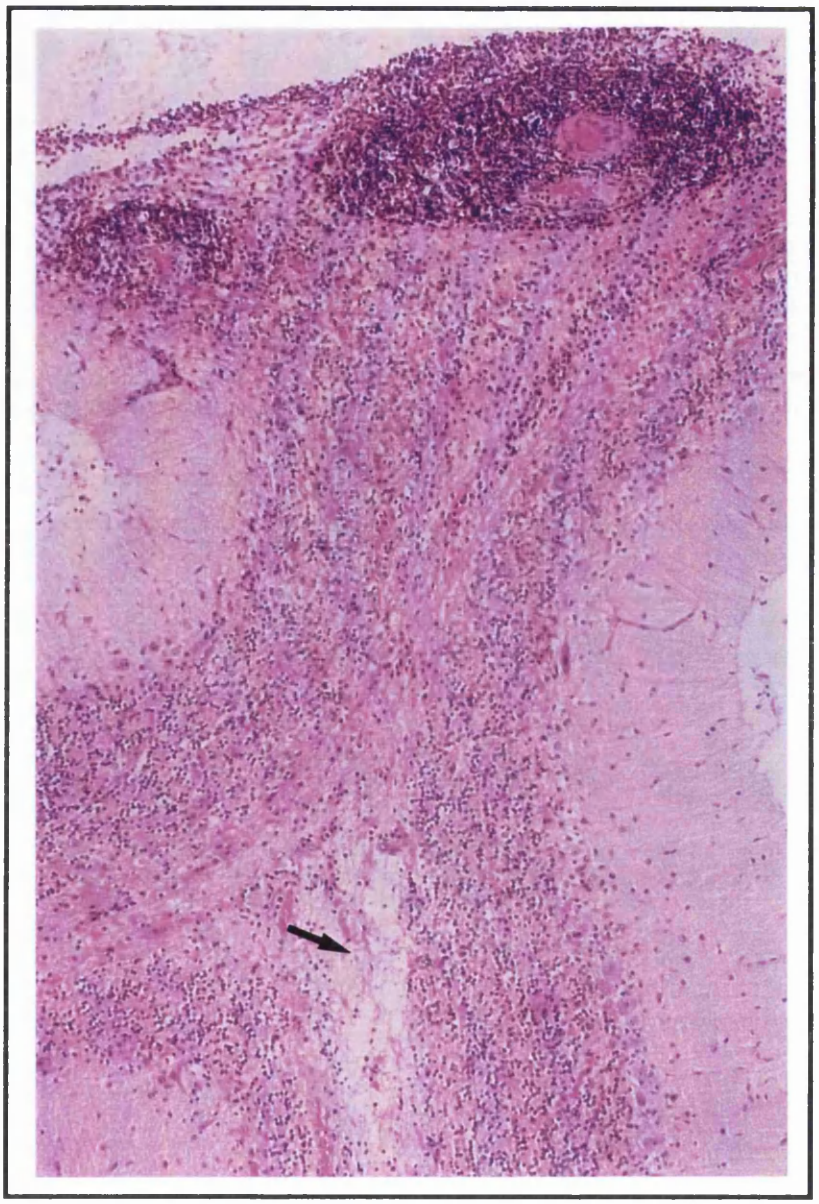

Figure 33.

Cerebellum, showing severe infiltration of inflammatory cells into cerebellum and necrosis of cerebellar tissue (arrow). (H&E, x 110)

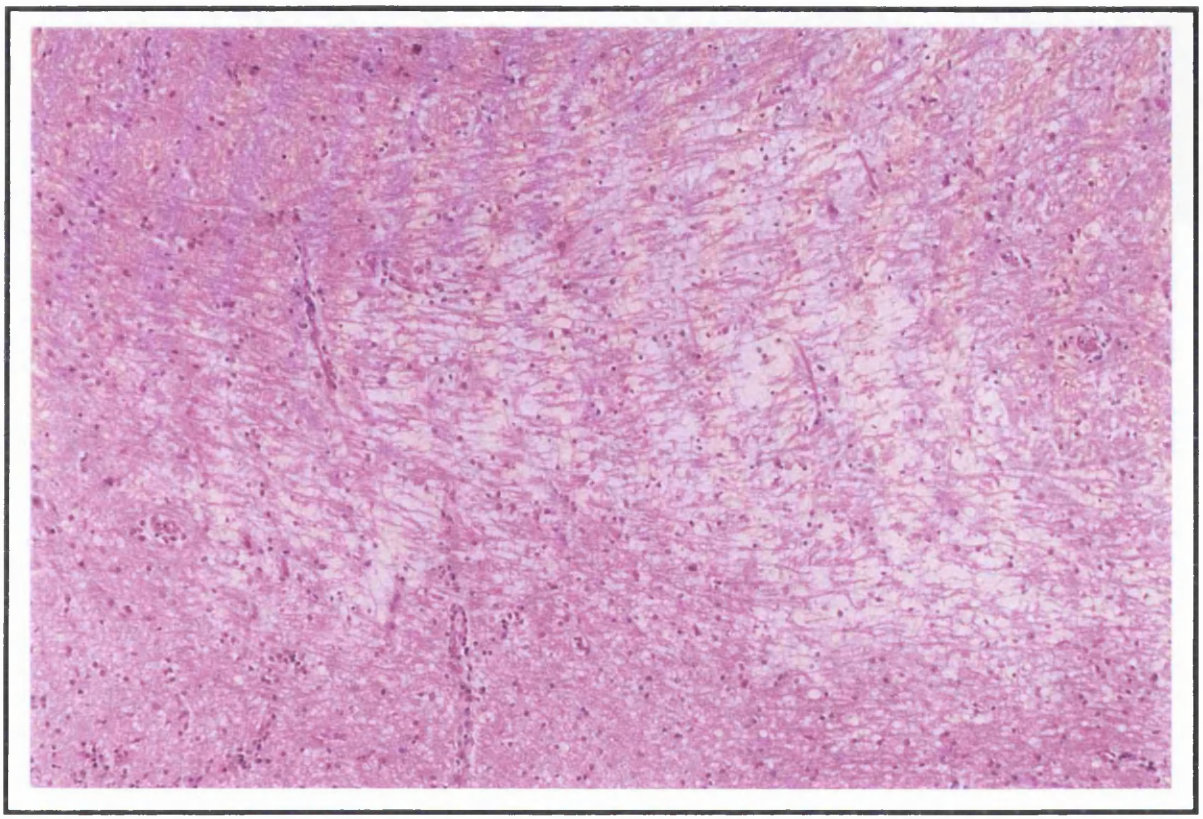

Figure 34.

Cerebellar white matter, showing necrosis. (H&E, x 110)

2.2.4.2. FSE

Two cases of FSE were diagnosed in this study. The history, clinical and laboratory findings of the first case are recorded in detail. As the histopathological findings were similar in both cases, they are combined and reported together following the case summaries.

Case 12: No. 131333

Signalment : Splodgy, 9.5 year old female Domestic Short-haired cat, BW 4 kg

This cat was presented with a 2 month history of behavioural changes, including an increase in the amount of time sleeping and sleeping in strange places, such as on the bannister. The cat became very timid and began to sway and stumble. The owner did not think the ataxic gait was worsening. The cat had difficulty in using the litter-tray, as if she was frightened of the tray and ran away from it. The other cat in the house was normal. Splodgy also began to dislike the other cat to get near to her. Moreover, she stopped self-grooming. The owner also described a strange episode, lasting about 10 seconds, with wide pupils, head flexed to one side and non-responsive. The cat was not vaccinated and serology to FIV and FCoV antibodies, and FeLV antigen were negative. There was no improvement following steroid injection.

Clinical examination revealed hypersalivation and staining by food around the mouth and nose. Neurological examination revealed head tremor and intention tremor, hyperaesthesia, wide-based stance, generalised ataxia, hypermetria, and a crouched posture with frequent falling. Other abnormalities included variable tactile and visual placing responses, slow reflex stepping and slow onset in hopping, especially in the forelimbs. The forelimbs were hypertonic (increased resistance in flexion). All spinal reflexes were slightly exaggerated. Cranial nerve examination showed dilated pupils, with normal menace response and pupillary reflexes.

Routine haematology revealed a mild, non-regenerative anaemia (Hb 9.5 g/dl, HT 26.5%). Repeat haematology, the following day, revealed a marked non-regenerative anaemia (RBC 4.05 $x10^{12}$/l, Hb 5.9 g/dl, HT 17.9%) and lymphopaenia (0.44 $x10^{9}$/l). Biochemistry showed elevated glucose (10.4 mmol/l), cholesterol (8.97 mmol/l), ALKP (169 U/l), AST (87 U/l) and ALT (217 U/l). Toxoplasma antibody titre was 8 i.u./ml. T_4 was normal (27 nmol/l). Thoracic radiographs did not show any abnormalities. CSF collected from the cerebellomedullary cistern revealed normal white cell count and protein level at 100 mg/l. Blood sampling a week later revealed unremarkable haematology but similar changes in the biochemistry: glucose (9.6 mmol/l), cholesterol (9.3 mmol/l), ALKP (158 U/l), AST (75 U/l) and ALT (149 U/l). The cat was discharged with a trial treatment of prednisolone (Prednicare®, Animalcare Ltd.).

However, she failed to respond to treatment and deteriorated over the next two months. The cat became so ataxic that she was unable to stand and had to be hand-fed. The owner requested euthanasia at this stage. Post-mortem examination was performed, with no gross abnormalities detected. Histopathological examination was characteristic of FSE.

Case 13: No. 134380

Signalment : Dude, 6.5 year old male Domestic Short-haired cat, BW 4 kg

This cat was presented with one month history of behavioural change which included increased nervousness, stopping roaming, aggression, tending to hide in dark places (i.e. under beds, hole in porch), stopped self-grooming, and appearing scared. Frequent episodes of sneezing and salivation, hyperaesthesia to sound, visual and tactile and dilated pupils were observed by the owners. Moreover, the other cat started bullying him. Staggery gait and falling over developed 1 week after the behavioural changes and progressed rapidly. There was no response to steroid or antibiotics given by the referring veterinary surgeon.

Clinical findings included hypersalivation, intermittent pupillary dilation, moderate cerebellar ataxia, and fine generalised tremor. The cat appeared very timid, and showed hyperaesthesia to all stimuli. Decreased conscious proprioception of the left hind limb was detected. Laboratory findings showed mild non-regenerative anaemia (haematocrit 24.8 %, haemoglobin 8.5 g/l), mild lymphopaenia and monocytosis. Serology was negative to FCoV, FIV and *T. gondii* antibody, and FeLV antigen. CSF analysis from the lumbar cistern revealed 3 WBC/mm^3, and marked elevation of protein at 1150 mg/l. Due to the poor prognosis, the owner elected euthanasia. Post-mortem examination was unremarkable and histopathology confirmed a diagnosis of FSE.

Pathology

Sections were examined from areas representing various regions of the brain of both cats. Severe vacuolation of the grey matter neuropil and/or neurones was evident. This extended throughout many brain stem nuclei, for example, the caudate nuclei, septal nuclei and medial geniculate body (Figure 35). Vacuolation was also evident in the deeper layers of the cerebral cortex. Vacuolation was also present in some white matter tracts. This vacuolation may well represent Wallerian degeneration as occasional macrophages were present in the white matter vacuoles. In the cerebellum, vacuolation was evident most predominantly in the granule cell layer, the interface between the granule cell layer and Purkinje cell layer, and to a lesser extent, in the molecular layer and deep cerebellar white matter (Figure 36). Neuronal vacuolation was

also evident particularly in certain medullary nuclei, such as the vestibular nuclei. The rounded vacuoles varied in size, from a single large vacuole to several small vacuoles within the cell body. The majority of vacuoles were empty although some contained lightly eosinophilic globular bodies. A glial reaction involving astrocytes and microglia was present. PrP immunostaining was positive (Figure 37).

Discussion

Many features in these two cases were in agreement with the literature (Pearson *et al.* 1993). Both cats were middle to old age, domestic short-haired cats. This was consistent with the literature that the mean age of affected cats was 6 years (with a range of 2-10 years) and the majority were non-pedigree. The first sign that their owners recognised was a change in behaviour. This was manifested as increased timidity with family members or other cats, with a tendency to hide and avoid contact (both cases). Aggression was also reported in Case 13, which could be fear-induced. Alteration in grooming behaviour was present in both cats. The ataxia seemed to occur later than the behavioural changes and was progressive. Other common clinical signs included hypersalivation, hyperaesthesia, and dilated pupils. There was no response to steroid or antibiotics. The history and neurological examination were suggestive of a progressive disease involving the forebrain (behavioural changes) and the cerebellum. These findings were consistent with FSE although other differential diagnoses such as FIP infection, inflammatory CNS disorders, diffuse lymphoma, trauma, intoxication, thiamine deficiency and metabolic disorders should be considered. Infection by FIP, FIV, FeLV and *Toxoplasma gondii* were ruled out by negative serology in both cases, although the marked elevation of CSF protein level of Case 13 could not be explained. Inflammatory disorders were unlikely, based on a normal CSF white cell count. Thiamine deficiency was not suspected as raw fish was not a component of the diet. There was no history of trauma or likely access to lead. Although Case 12 had elevated liver enzymes, albumin and urea levels were normal with lack of systemic illness, thus it was unlikely to be a hepatic encephalopathy. Diffuse lymphoma was ruled out on microscopic examination of the brain.

The common haematological abnormality was a non-regenerative anaemia. However, this was only an intermittent finding in Case 12 and was not a common finding reported in the literature.

Demonstration of characteristic neuronal vacuolation on histopathological examination and positive prion protein immunostaining provided the definitive diagnosis of FSE in both cases. The cats affected with FSE show behavioural changes and cerebellar ataxia initially, which may suggest that these relevant areas (i.e. basal nuclei, and cerebellum) are more susceptible to

prions and may be affected before the rest of the brain. Pearson *et al.* (1993) reported that vacuolation of the neuropil was consistently more severe in some areas which included the medial geniculate body in the mid-brain, the thalamus, the corpus striatum, the cerebellar and deeper layers of the cerebral cortex. The raphe nucleus, the dorsal nucleus of the vagus nerve, the vestibular nuclei, and the red nucleus are predilection areas for neuronal vacuolation. Some of these findings were consistent with the present study.

Antemortem diagnosis may be possible by screening for scrapie-associated fibrils and modified PrP in lymphoreticular tissues, such as lymph nodes or tonsils. However, since cats are unlikely to be the natural host for the agent responsible for FSE and are probably dead-end hosts, involvement of extraneural tissues may be limited (Gruffydd-Jones *et al.* 1991).

The agent causing FSE is thought to be the same as the BSE agent from transmission studies, based on similar ranking of incubation periods and lesion profile in mice (Fraser *et al.* 1994). This suggests a bovine origin feeding source for FSE, rather than scrapie (Anon 1995). Bruce *et al.* (1997) also concluded that the cause of BSE, FSE, TSE of exotic ruminants, and new variant Creutzfeldt-Jakob disease (vCJD) is the same strain of agent. The two cats reported in this study were probably exposed to BSE affected material in their diet, before the specified offal ban was extended to forbid use of 'specified bovine offal' materials in proprietary pet foods. Since the cat is an unnatural host, natural spread between individuals is believed to be unlikely (Gruffydd-Jones *et al.* 1991).

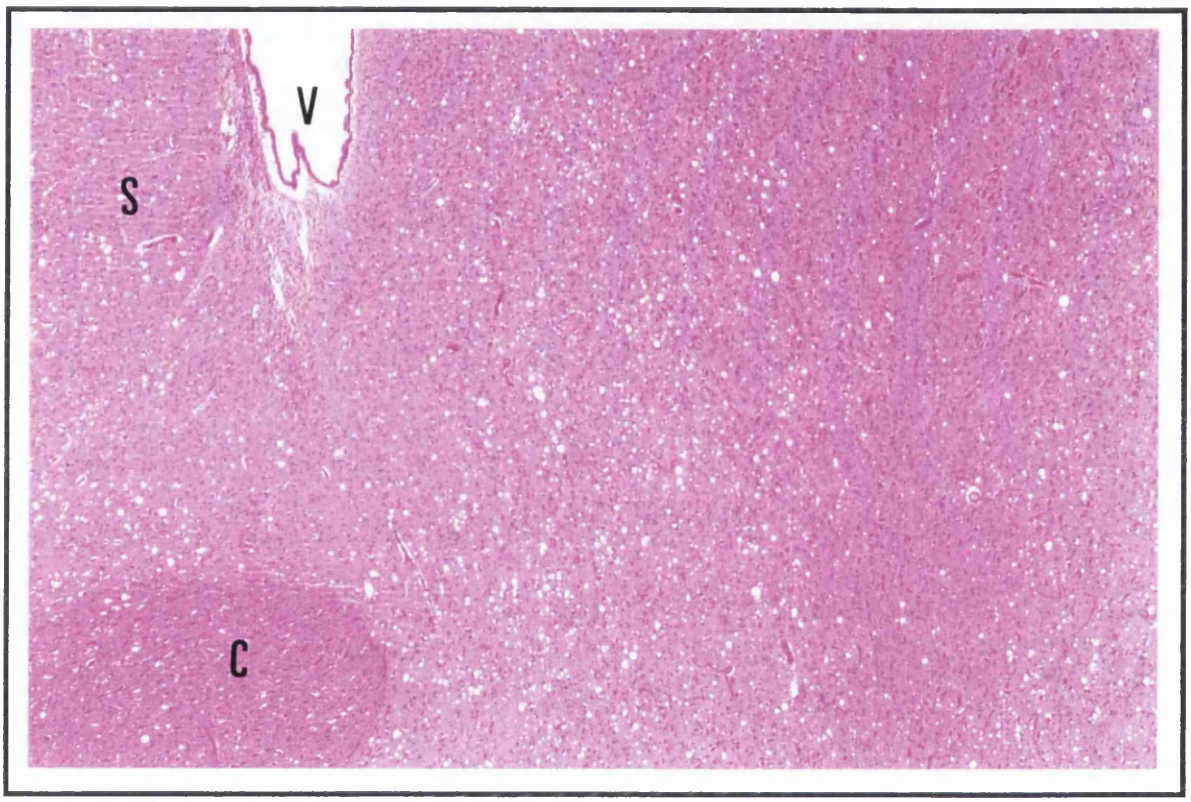

Figure 35.

Case 12. Area of forebrain adjacent to lateral ventricle (V), anterior commissure (C), and septal region (S). A generalised vacuolation of neuropil is present. (H&E, x 44)

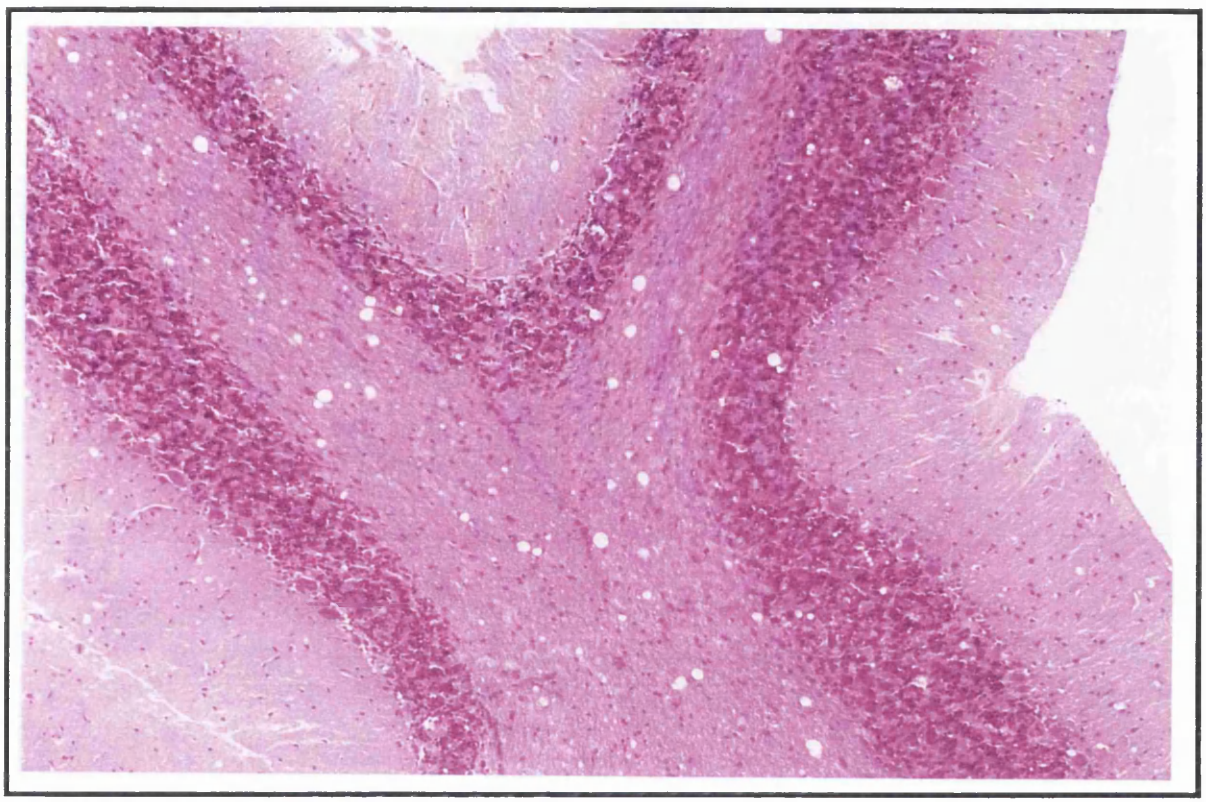

Figure 36.

Cerebellum, showing vacuolation in granule cell layer and white matter of folium. (H&E, x 110)

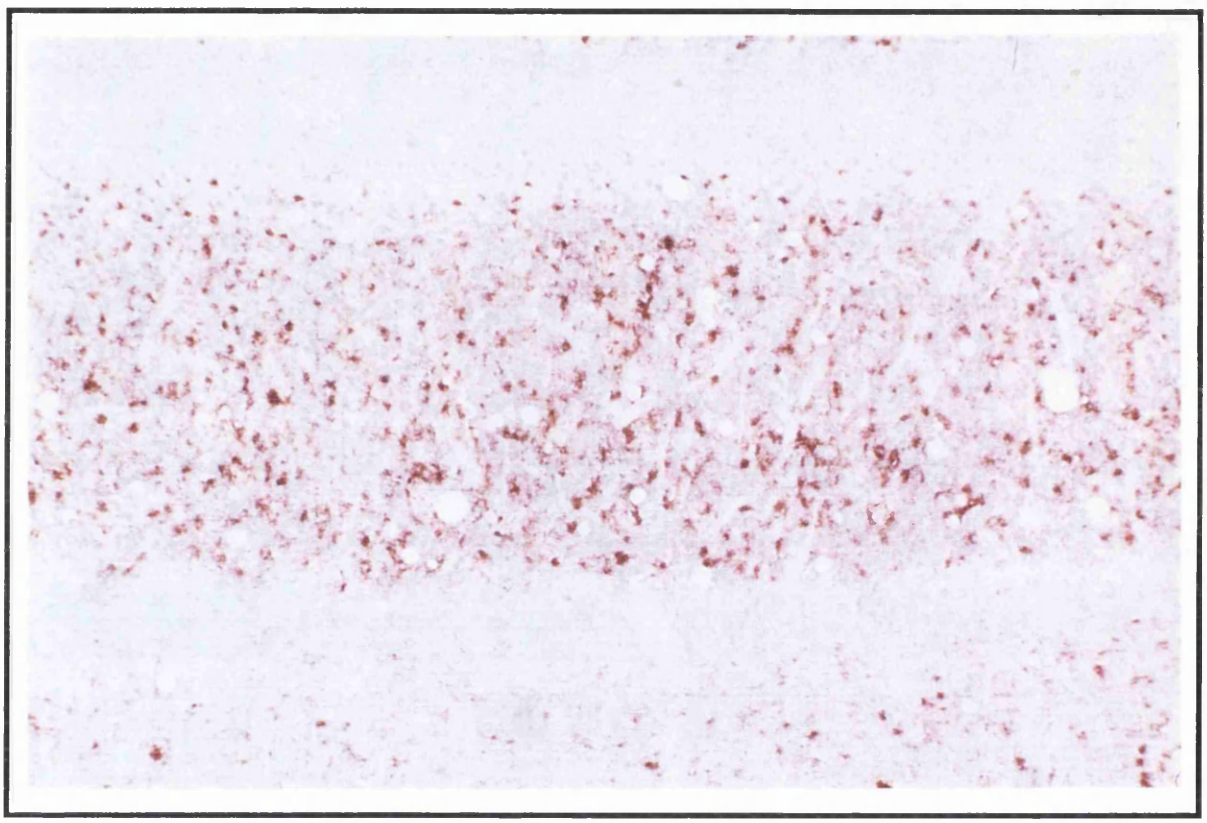

Figure 37.

Cerebellar cortex, showing positive PrP immunostaining, predominantly in granule cell layer. (PrP immunostaining, x 145)

2.2.5. INFLAMMATORY CEREBELLAR DISEASE: STEROID- RESPONSIVE TREMOR SYNDROME

In this series of studies, the steroid-responsive tremor syndrome was diagnosed in 10 out of 25 cases (Cases 14-23). The clinical details are summarised in Table 9.

"Steroid-responsive tremor syndrome" (SRTS) is used in this category of cerebellar disease because the main clinical sign was characterised by a degree of generalised and/or intention tremor as the dominant part of the cerebellar signs, and all responded to treatment with steroid and in some cases, a combination of steroid and diazepam (Approved Prescription Services Ltd.).

Discussion

In this study, steroid-responsive tremor syndrome is the most frequently encountered disease which affects the cerebellum. As all cases were treated by medication, no pathology is available, thus only a tentative diagnosis can be made. Only dogs were affected in this series and they were 5 years of age or younger, small to medium sized (<15 kg) pure-bred dogs which was a consistent finding with Wagner *et al.* (1997). The breeds which appeared most commonly affected were the West Highland White Terrier (4 cases) and Yorkshire Terrier (3 cases). Maltese (1 case) and Miniature Poodle (1 case) also have been reported in the literature (Bagley *et al.* 1993, Wagner *et al.* 1997), but the English Springer Spaniel dog (1 case) has not been previously reported. Previously, this disease was termed "Little white shakers" syndrome, because dogs with white coats are commonly affected, however, dogs of any colour, size or breed can also be affected (Parker 1991, Wagner *et al.* 1997). In the present study, half of the dogs affected had a white coat (4 West Highland white Terriers, 1 Maltese), and the English Springer Spaniel dog was black and white.

Acquired generalised tremors in dogs can be caused by intoxications (e.g. organophosphates, hexachlorophene, bromethalin), drugs (fentanyl/droperidol, epinephrine, isoproterenol, sodium valproate, 5-flurouracil), inflammatory CNS disease or idiopathic (Bagley 1991). However, in the present study, there was no history that the dogs were exposed to toxins or drugs.

The majority of cases had an acute onset of clinical signs from several days' to several weeks' duration. There was no history of access to toxins or mycotoxins which was reported causing severe generalised tremor in dogs (Wagner *et al.* 1997). Clinical findings were consistent with a diffuse cerebellar disease, or multifocal brain disease, although some lateralised signs may be seen, as in Cases 16 and 21. All cases showed a degree of generalised tremor and/or intention

tremor, which became worse with excitement, and disappeared during sleeping. Common concurrent clinical signs included depression, seizures, vestibular signs, and reduced gag reflex.

Routine haematology and biochemistry were performed in most cases (except Cases 14, 16, 19) but did not reveal significant abnormalities and are thus not reported here. CSF collected from the cisterna magna may indicate an inflammatory nature, with an increase in the number of white cell count (Cases 14, 16, 20, 22), protein (Case 19), or both (Cases 17, 18). However, this may not be necessary, as in Cases 15, 21 and 23, the CSF analyses were normal. In Case 21, this may be the result of steroid administration by the referring veterinarian prior to CSF tap (Wagner *et al.* 1997). In Case 15, the repeated CSF sampling was performed after steroid treatment for a week. Clinically, the dog had improved markedly and the normal CSF analysis was probably the consequence of steroid administration. Although CSF did not suggest an inflammatory cause in Case 23, the dramatic response to steroid and diazepam treatment indicated that SRTS was the most likely diagnosis. In addition. Wagner *et al.* (1997) have reported that some SRTS cases have normal total white blood cell count in CSF but an abnormal distribution of WBC types.

In those cases in which a cytospin was performed on the CSF, cytology revealed predominantly lymphocytes (Case 14 & 16), a pleiocytosis (Case 22) and occasionally atypical mononuclear cells (Case 17). In the majority of the cases, the protein level was within normal reference, however, Cases 17 and 18 had raised protein levels with increased WBC count. CSF analysis of Case 19 showed a raised protein level with normal WBC count.

Only a tentative diagnosis was achieved in these cases. An aetiological agent was not apparent. Cerebrospinal fluid antibody titres to CDV were determined in Cases 21 and 23, and these dogs were seronegative, which ruled out CDV infection. Neospora titre was negative in Case 18. In cases where a cytospin was performed on the CSF, no organisms were found, which made infection unlikely. The underlying disease process in SRTS is not well understood, however, an inflammatory or immune-mediated cause is highly suspected due to the response to steroid treatment. Histopathological examination of dogs with SRTS may be normal, or may reveal a diffuse, mild meningoencephalomyelitis, characterised by lymphocytic infiltrates and perivascular cuffing, which may be most apparent in the cerebellum but not confined to it (Farrow 1986). However, all cases in this series were clinically normal after treatment and no necropsy was performed. If available, CT or MRI may demonstrate an abnormal enhancement pattern suggestive of inflammatory changes.

In this series, all cases responded favourably to medical treatment of prednisolone or a combination of prednisolone and diazepam. The dosage used in this study was prednisolone 1-3

mg/kg/day and diazepam 0.5 mg/kg q8-12h. In the literature, immunosuppressive doses of steroid are used at 2-4 mg/kg/day. The present study may suggest that anti-inflammatory doses of steroid can be as effective as immunosuppressive doses, preferably in combination with diazepam. A prolonged course of treatment was utilised, varying from 5 weeks to 13 weeks, depending on the response of the individual animal. A complete recovery was achieved in every case, confirmed either by re-examination and/or phone consultation. In the majority of cases in this study, several weeks of therapy were required. Recurrence of the problem has not been encountered in any case, but has been reported in the literature (Farrow 1986).

Table 9. Details of 10 cases with steroid-responsive tremor syndrome

Case No.	Breed (BW)	Age/ Sex†	Presenting signs and use of steroid prior to presentation‡	Clinical findings✞	Laboratory findings✞	Treatment and response (starting dose)
14 (130321)	Yorkshire Terrier (1.4 kg)	5y F	6 wk history of dullness, depression, could not walk up stairs, stumbling, lost balance, a vague history of fly-catching & appearing vacant	Depression, generalised ataxia especially hind limbs, intention tremor, ↓conscious proprioception (CP) in all limbs, ↓menace response (MR) in right eye	CSF: 102 WBC/mm^3 Cytology: predominantly lymphocytes and some reactive lymphocytes (plasmacytoid) Inadequate sample for protein analysis	Dexamethasone and then a tapering course of prednisolone (1.5 mg q12h) for 8 wk. Improvement 2 wk later, lost to follow up.
15 (132423)	Yorkshire Terrier (3 kg)	3y F	Acute onset of several episodes of seizures 4 wk ago, progressed to trembling & ataxia so severe that the dog could not walk	Generalised ataxia, hypermetria, wide-based stance, generalised tremor, intention tremor, falling, ↓unconscious proprioception (UCP), bilateral absence of MR, right eye ventrolateral strabismus	Inadequate CSF sample for analysis initially Repeated CSF sampling after treatment for 1 wk: 4 WBC/mm^3, protein 180 mg/l	A tapering course of prednisolone (5 mg q12h) for 5 weeks. No seizures since treatment started, clinically normal 6 wk after.
16 (132499)	West Highland White Terrier (9 kg)	1.5y M	Acute onset crying in pain for 4 d, trembling, falling over to right frequently, intermittent jaw-champing, seizure Steroid: Dexamethasone	Depression, ataxia, leaning & falling to right, body curved to right, ↓UCP, bilateral absence of MR, rotatory nystagmus, intermittent ocular tremor, absent gag reflex, intermittent jaw-champing	CSF: ↑WBC count Protein: 110 mg/l Cytology: lymphocytes (92%), neutrophils (6%), macrophages (2%)	Respond to prednisolone (10 mg q12h) initially, but developed marked generalised tremor & ataxia. Improved on diazepam (5 mg q12h) & prednisolone (5 mg q12h), clinically normal 12 wk later.
17 (132692)	West Highland white Terrier (8 kg)	5y F	Lethargy, had difficulty in jumping up 1 m ago, progressed to ataxia, truncal sway, falling over, misjudging distance, head tremor, 2 "panic attacks" during which the dog appeared scared, not recognising owner, passed urine & faeces	Generalised tremor, mild ataxia, hypermetria, ↓UCP of fore limbs, ↓MR & gag reflex, ocular tremor Fundoscopic examination revealed several small grey areas suggestive of inflammatory origin	CSF: 93 WBC/mm^3 Cytology: atypical mononuclear cells appeared histiocytic in origin (59%), lymphocytes (38%), neutrophils (2%), macrophages (1%), occasional macrophages showed erythrophagocytosis. Protein: 370 mg/l Chest, abdominal radiography, bone marrow examination normal. Repeated CSF sampling 1 wk later: 16 WBC/mm^3, with 62 % lymphocytes, 33% histiocytic cells, 3% macrophages, 2% neutrophils.	A tapering course of prednisolone (10 mg q12h) for 9 wk after the second CSF sampling. The dog was clinically normal 8 wk after treatment started.

18 (133813)	Miniature Poodle (2.25 kg)	3m F	1 wk history of dullness, coughing, intermittent seizures, personality change (bite people), ataxia, rocking movement of head laterally.	Generalised ataxia, hypermetria especially of hind limbs, generalised tremor, intention tremor, ↓UCP, bilateral absence of MR	CSF: 65 WBC/mm^3 Cytology: lymphocytes (62%), macrophages (28%), neutrophils (9%), eosinophils (1%). Many lymphocytes have azurophilic granules (T-cells) and some appear reactive. Protein: 350 mg/l	A tapering course of prednisolone (2.5 mg q12h) for 8.5 wk. Clinically normal 2 wk after treatment started.
19 (133880)	Yorkshire Terrier (7.6 kg)	2.5y M	3 d history of acute onset of hind limb ataxia & arched back Steroid: Dexamethasone	Generalised ataxia, hypermetria especially hind limbs, falling over, mild intention tremor, ↓MR	CSF: 2 WBC/mm^3 Protein: 300 mg/l Negative serum antibody titre to *Neospora caninum*	A tapering course of prednisolone (5 mg q12h) for 5.5 wk. Clinically normal 6 wks after treatment started.
20 (133905)	West Highland White Terrier (9.25 kg)	15m FN	4 d history of acute onset of nervousness, depression, trembling, involuntary twitching movements, loss of balance, vomited several times Steroid: Dexamethasone	Mild depression, generalised tremor, mild ataxia	CSF: 8 WBC/mm^3 Protein: 130 mg/l	A tapering dose of prednisolone (5 mg q12h) & diazepam (5 mg q8h) for 13 wk. Owner reported the dog was back to normal 12 wk after treatment.
21 (134359)	English Springer Spaniel (15.25 kg)	18m M	18 d history of acute onset of vomiting, inco-ordination, generalised tremor, falling over, horizontal nystagmus, head tilt & circling to left Steroid: Dexamethasone	Severe generalised tremor, exaggerated head & neck movements, ataxia, left head tilt, ↑muscle tone & patellar reflex, spontaneous changing vertical & rotatory nystagmus, abnormal vestibulo-eye movements, ventral strabismus of left eye, mild anisocoria, ↓gag reflex. When lying on back, developed a rapid vertical & rotatory changing nystagmus & a rigid extension posture, very disorientated for 2-3 minutes	CSF: 4 WBC/mm^3 Protein: 120 mg/l Negative antibody titre to CDV in CSF	A tapering dose of prednisolone (10 mg q12h) & diazepam (7.5 mg q12h) for 7 wk. Dog was clinically normal 4 wk after treatment was started.
22 (134669)	Maltese (2.75 kg)	5y FN	5 wk history of acute onset trembling, could not manage stairs, no improvement to diazepam	Severe generalised tremor especially head, moderate ataxia, wide-based stance, hypermetric hind limb gait, ↓UCP, mild ventrolateral strabismus of left eye, ocular tremor	CSF: 6 WBC/mm^3, slight RBC contamination Cytology: lymphocytes (46%), neutrophils (32%), macrophages (22%) Protein: 150 mg/l	A tapering course of prednisolone (1.5 mg q12h) & diazepam (1.5 mg q12h) for 5 wk. Markedly reduced tremor 2 d after treatment started, clinically normal 4 wk post-treatment.

23 (134725)	West Highland White Terrier (7.5 kg)	20m F	4 wk history of reluctance to stand up on hind limbs, 1 wk mild tremor progressed to marked generalised tremor, could not jump up, fell over occasionally, more timid, less confident in going down stairs, lost interest to other dogs	Generalised tremor, mild wide-based stance of hind limbs, gait relatively normal	CSF: 3 WBC/mm^3, slight contamination with RBC (47/mm^3) Protein: 130 mg/l Negative antibody titre to CDV in CSF	A tapering course of prednisolone (7.5 mg q12h) & diazepam (5 mg q12h) for 5.5 wk. Owner reported markedly reduced tremor 2 d after treatment started, and the dog was clinically normal 2 wk later.

Key: † y: year(s), m: month(s), F: female, M: male, N: neutered

‡ wk: week(s), d: day(s)

✞ ↓: reduced or decreased, ↑: raised or increased

✦ CSF: cerebrospinal fluid, WBC: white blood cell, RBC: red blood cell

2.2.6. MISCELLANEOUS

There were two cases in this study in which no probable diagnosis could be reached. Possible diagnoses include trauma, inflammation or ischaemic incident causing predominantly cerebellar signs, and concurrent vestibular signs. These two cases are reported in detail.

Case 24: No. 132809

Signalment : Pip, 4 year old neutered female Domestic Short-haired cat

This cat was presented with a 2 week history of acute onset of ataxia after being let out of the house to roam. The cat was normal prior to the morning walk and came back to the house 4 hours later, vomited once and was very wobbly. The referring veterinary surgeon noticed that the cat had nystagmus and was staggering to the left. Antibiotics and steroid injections were given. On the following day, the cat deteriorated becoming generally ataxic and the horizontal nystagmus was more obvious. The cat started to show gradual improvement 3 days after the initial incident. Apart from inco-ordination, the owner also noticed other clinical signs such as head bobbing and swaying gait which were worsened by excitement. The cat was not able to jump up.

On examination in the GUVS, the cat showed severe generalised ataxia and wide-based stance. There was excessive backwards and sideways movement of the head and neck, which appeared to be disoriented in space. Head bobbing was obvious. The cat was bright, alert and responsive. No weakness or conscious proprioceptive deficits could be detected. The righting reflex was normal. Cranial nerve examination revealed reduced menace response, and absence of vestibular-eye movement. There was no spontaneous or positional nystagmus. The clinical signs were suggestive of a diffuse cerebellar problem with concurrent vestibular signs. Based on the acute onset of clinical signs and gradual improvement, the differential diagnoses should include trauma, inflammation, or ischaemia.

In view of the continuous improvement, no investigation was pursued. A tapering course of steroid therapy was prescribed. The cat was re-assessed 3 and 5 weeks after the incident and showed gradual improvement. The cat could climb up stairs and started grooming. She was not able to sharpen her claws on the third-week visit but could do so on the fifth-week check-up. There was less marked head bobbing, unless the cat was very excited. Ataxia was reduced and the cat could walk reasonably well. The vestibular-eye movement started to reappear on the fifth-week check-up, although it was still abnormally slow.

Nine months after the onset of clinical signs, the cat returned for re-examination. The owner reported that the cat improved and coped very well, although there were still some abnormal head and neck movements. On observation, the gait was not ataxic, but there was a mild degree of head and neck ataxia. The vestibular-eye movements were normal bilaterally.

Case 25: No. 134457

Signalment : Bono, 8.5 year old male German Shepherd dog, BW 35 kg

This dog was presented with a history of acute onset of ataxia and falling over the previous night. Treatment at the referring veterinary surgeon included dexamethasone 5 mg, acetylpromazine (ACP) 0.3 mg, and vitamin B_{12} injections.

Clinical examination revealed a melanoma on the dorsolateral limbus of the left eye. Neurological examination revealed severe ataxia, a right-sided hypermetric gait, a wide-based stance of hind limbs, and a left head tilt. The dog tended to lean and fall over to either side while standing. Conscious proprioception (paw positioning) was reduced in the right hind limb, and the response was hypermetric in the right fore limb. Hopping was delayed in onset but exaggerated in response in both hind limbs. Reflex stepping was reduced in both hind limbs. Cranial nerve examination revealed an intermittent left ventral strabismus. The ataxia, right-sided hypermetric gait, and the left head tilt were features of paradoxical vestibular syndrome. A poor prognosis was given to the owner.

Unexpectedly, the dog improved markedly within 24 hours and showed much less ataxia. The left head tilt disappeared and a right head tilt was present instead. The right-sided hypermetric gait was also reduced, although hopping was still delayed and exaggerated in the right hind limb. Paw positioning in the right hind limb was slightly slow, but was an intermittent finding. Cranial nerve examination revealed a right ventral strabismus.

Haematology showed a neutrophilia and biochemistry demonstrated a slightly low potassium (3.1 mmol/l) and elevated cholesterol (9.06 mmol/l). Basal cTSH and T_4 concentrations were within the reference range, making primary hypothyroidism unlikely. Thoracic radiographs (inflated left and right chest) showed no abnormalities, such as metastases. Cisterna magna CSF analysis was normal (no white cells, protein 220 mg/l). There was no significant titre to canine distemper virus in the CSF. Repeated haematology was unremarkable.

The dog was discharged on a tapering course of prednisolone (15 mg q12h for 2 days, then q48h for 10 days). Re-examination was performed about 3 weeks after treatment started, and the owner reported that the dog gradually improved and returned to normal. Only very

occasionally the dog lost balance of the hind limbs when he was turned sharply. Neurological examination revealed a slightly low-based stance of the hind limbs. The dog was minimally slow on hopping of the hind limbs. Cranial nerve examination showed no abnormalities. The head tilt and strabismus had resolved completely.

Discussion

Both cases were presented with acute onset of cerebellar and vestibular signs. In both instances, dexamethasone was given by the referring veterinary surgeons, and the response to the steroid may indicate an inflammatory-type disease, or possibly ischaemia or trauma, in which the steroid reduced the peri-lesional oedema. Intoxication is another possible cause. No investigation (such as CSF tap) was performed in the cat, and even if it had been performed, it is highly likely that the result would have been normal, due to the previous use of steroid.

The prolonged and incomplete recovery of the cat means that there is still some cerebellar and vestibular dysfunction. Trauma or ischaemia may cause more permanent and severe damage to the cerebellum, and may suggest this is the main cause of cerebellar dysfunction in this cat.

The dog was presented with paradoxical vestibular syndrome, which strongly suggested a mass lesion in the caudal cerebellar peduncle, flocculonodular lobe or cerebellar medulla. Most common causes are neoplasia and GME, however, haemorrhage and oedema may also resemble a mass. The initial clinical signs were suggestive of a mass lesion in the right cerebellum. However, 24 hours later, the right head tilt and ventral strabismus were more suggestive of a right vestibular problem instead. One explanation is that both the right cerebellum (i.e. flocculonodular lobe, or cerebellar peduncle) and the right vestibular nuclei are involved, and the disease process in the cerebellar peduncle resolved, possibly following steroid treatment, leaving the right vestibular signs. Ischaemia or inflammation are the most likely diagnose in this dog.

In both cases, imaging of the cerebellum, such as MRI or CT, might have been helpful in aiding diagnosis.

SECTION III.

GENERAL DISCUSSION

The majority of cases in this series can be grouped according to the aetiologies by the DAMNIT system. Although cerebellar diseases affect both dogs (14 cases) and cats (11 cases), the distribution of the disease varies. In the dog, the most frequently encountered cerebellar disease was steroid-responsive tremor syndrome (10 cases, Cases 14-23), which is an inflammatory disease of unknown aetiology involving the cerebellum. Degenerative cerebellar disease was confirmed by histopathological examination in one dog (Case 1), while anomalous, neoplastic and a transient paradoxical vestibular syndrome probably caused by inflammation or angiopathy were tentatively diagnosed in three other dogs (Cases 8, 9 and 25). In the cat, developmental anomaly of the cerebellum was diagnosed clinically in 4 cats (Cases 4-7), with a presumption of cerebellar hypoplasia caused by panleukopaenia virus. Degenerative cerebellar disease occurred in 2 cats (Cases 2 and 3), and cerebellar abiotrophy and LSD were diagnosed, respectively, by histopathological examination. The most common infectious diseases involving the feline cerebellum were FIP (Cases 10 and 11) and FSE (Cases 12 and 13), in which both were diagnosed antemortem and confirmed by histopathology. Trauma or angiopathy was tentatively diagnosed in one cat (Case 24).

From the results of this series, diffuse cerebellar disorders are more commonly encountered in dogs and cats. Focal or lateralised cerebellar signs can be caused by neoplasia, angiopathy (i.e. infarction, embolism or haemorrhage) or trauma. In this series, lateralised cerebellar signs were seen in only one dog (Case 9), showing paradoxical vestibular signs, and based on the clinical and laboratory findings and the progression of the disease, a diagnosis of a tumour affecting the cerebellum was made. All other cases were showing diffuse cerebellar signs. In the degenerative group (Cases 1-3), pure cerebellar signs were shown in the early stage, although in the lysosomal storage cat (Case 3), more multifocal CNS signs were apparent in the advanced stage of the disease. All animals in the developmental anomaly group (Cases 4-7) showed diffuse cerebellar signs. The infectious group (Cases 10-13) showed multisystemic and/or multifocal CNS signs: the FIP cats (Cases 10 and 11) were systemically ill and showed multifocal CNS signs, whereas the FSE cats (Cases 12 and 13) were presented with behavioural changes and cerebellar signs. The majority of dogs in the inflammatory group showed multifocal CNS signs, although in a number of cases, only a diffuse cerebellar dysfunction characterised by tremor and mild cerebellar ataxia was seen.

In the majority of cases, a definite diagnosis could not be made on the basis of history and clinical findings. CSF analysis is most valuable in ruling in an inflammatory cause. If available, MRI or CT may be useful in provide more information about the size of the cerebellum in cases of suspected cerebellar anomaly such as cerebellar hypoplasia in cats (i.e. Cases 4-7). In

addition, the presence of abnormal space-occupying lesions may be seen, that would provide a diagnosis quickly (i.e. if used in Case 9). CT or MRI may also aid diagnosis in cases where the lesions cannot be localised clearly, such as the dog with transient paradoxical vestibular syndrome (Case 25). And if abnormal mass(es) are detected, CT-guided stereotactic brain biopsy can be performed to aid diagnosis (LeCouteur *et al.* 1999). Without these advanced imaging techniques, one has to rely on clinical findings and CSF analysis. However, the latter is not ideal if a cerebellar neoplasm or severe meningoencephalitis is suspected, due to the increased risk of raised intracranial pressure, leading to brain herniation following general anaesthesia or CSF tap.

Treatment of the cerebellar diseases depends on the aetiology. Some of the diseases, such as degenerative cerebellar conditions, are untreatable at this stage of veterinary medical development, although some treatment regimes of LSD are under investigation. Some of the diseases, such as cerebellar anomaly, are non-progressive and thus require no treatment. Infectious diseases involving the cerebellum often carry a very poor prognosis despite appropriate and aggressive treatment. Neoplasms of the cerebellum may be resectable, with advanced equipment, technique and extreme caution, if the location of the tumour is amenable to surgery. Cerebellar signs caused by nutritional deficiency or toxicities may subside if appropriate treatment is instigated. Recovery of the cerebellum from traumatic insults depends on the severity of the damage and the compensatory capability of the individual animal. Response to treatment may vary in the category of inflammatory cerebellar diseases of unknown origin. In general, generalised tremor syndrome responded extremely favourably to steroid or preferably, a combination of steroid and diazepam, as documented in this study. GME, on the other hand, carries a poor prognosis, despite initial temporary improvement with steroid administration.

This study on cerebellar diseases in dogs and cats has described the more common cerebellar diseases referred to the GUVH. Other diseases involving the cerebellum which are presented in the literature review were not encountered during this study. This may indicate that they are less common in Scotland.

SECTION IV.

APPENDIX

4.1 REFERENCE RANGES FOR DOGS & CATS (GUVS)

4.1.1 Haematology

	Unit	Canine	Feline
RBC	x 10^{12}/l	5.5-8.5	5-10
Hb	g/dl	12-18	10-15
HCT	%	37-55	30-45
MCV	fl	60-77	39-55
MCH	pg	19.5-24.5	12.5-17.5
MCHC	g/dl	32-36	30-36
Platelet	x 10^9/l	200-500	300-800
WBC	x 10^9/l	6-12	5.5-15.5
neutrophils	x 10^9/l	3-11.8	2.5-12.5
lymphocytes	x 10^9/l	1-4.8	1.5-7
monocytes	x 10^9/l	0.15-1.35	0-0.85
eosinophils	x 10^9/l	0.1-1.25	0-1.5
basophils	x 10^9/l	0-0.06	0-0.06

4.1.2 Biochemistry

	Unit	Canine	Feline
Total protein	g/l	50-78	60-85
Albumin	g/l	29-36	26-36
Total globulin	g/l	28-42	27-45
Urea	mmol/l	2.5-8.5	2.7-9.2
Creatinine	umol/l	45-155	91-180
Total bilirubin	umol/l	0-10	0-10
Calcium	mmol/l	2.34-3.00	1.60-2.56
Phosphate	mmol/l	1.29-1.90	1.29-2.84
ALKP	u/l	0-230	0-100
AST	u/l	0-40	0-30
ALT	u/l	0-90	0-35
GGT	u/l	0-20	0-15
GLDH	u/l	0-10	0-10
CK	u/l	0-150	0-150
Na	mmol/l	136-159	145-160
K	mmol/l	3.4-5.8	2.6-5.2
Na:K	--	>27	>27
Cl	mmol/l	95-115	94-113
Cholesterol	mmol/l	2.0-7.0	1.8-5.2
Triglyceride	u/l	<0.6	<0.6
Amylase	u/l	0-3675	456-1376
Lipase	u/l	0-1004	0-450
Glucose	mmol/l	3.3-5.5	2.7-5.5
Thyroxine	nmol/l	15-60	15-50
cTSH	ng/ml	0.01-0.65	--

4.2 FIXATIVES

4.2.1 Buffered neutral formaldehyde (BNF) 4%

For 1 litre of fixative:

40% formaldehyde (Merck)	100 ml
Tap water	900 ml
sodium di-hydrogen phosphate	4 g
di-potassium hydrogen phosphate	8 g

4.2.2 Karnovsky's modified fixative (paraformaldehyde/glutaraldehyde 4%/5%)

For 500 ml fixative:

8% formaldehyde†	250 ml
25 % glutaraldehyde	100 ml
0.08 M cacodylate buffer‡	mix formaldehyde & glutaraldehyde,
pH 7.2	make up to 500 ml
Calcium chloride	250 ml

†: Add 20 g paraformaldehyde to 250 ml distilled water; heat to 65°C; add 1 M sodium hydroxide (NaOH) to clear the solution; cool to 4°C.

‡: Add 17.12 g sodium cacodylate buffer to 1 litre and adjust pH to 7.2.

Filter and store at 4°C for a maximum of ~ 14 days.

4.3 TISSUE PROCESSING PROTOCOLS

4.3.1 Paraffin wax processing

Solutions used for preparation of tissue for paraffin blocks:

1)	70% methylated spirit/ 5% phenol	2 hrs
2)	90% methylated spirit/ 5% phenol	2 hrs
3)	methylated spirit	2 hrs
4)	ethanol/ 5% phenol x 3	2 hrs
		1 hr
		1 hr
5)	1% celloidin in methyl benzoate*	4 hrs
6)	xylene	1 hr (x3)
7)	paraffin wax x 2	7 hrs

* celloidin was obtained as Necoloidine (Merk) and considered as a 100% solution (1 ml in 100 ml benzyl benzoate).

4.3.2 Resin processing

Processing involved the following solutions:

1)	Isotonic cacodylate buffer†	4°C	50 mins
2)	1% osmium tetroxide in cacodylate buffer	room temperature	2 hrs
3)	Isotonic cacodylate buffer	room temperature	30 mins
4)	50% ethanol	4°C	5 mins
5)	50% ethanol	4°C	10 mins
6)	70% ethanol	4°C	5 mins
7)	70% ethanol	4°C	10 mins
8)	80% ethanol	4°C	5 mins
9)	80% ethanol	4°C	10 mins
10)	90% ethanol	4°C	5 mins
11)	90% ethanol	4°C	10 mins
12)	ethanol	4°C	20 mins
13)	ethanol	4°C	20 mins
14)	propylene oxide	room temperature	15 mins
15)	propylene oxide	room temperature	15 mins
16)	1:3 resin*: propylene oxide	room temperature	13 hrs
17)	1:2 resin: propylene oxide	room temperature	6 hrs
18)	1:2 resin: propylene oxide	room temperature	18 hrs
19)	resin	30°C	4 hrs

† Isotonic sodium cacodylate buffer:

16.05 g	sodium cacodylate
3.8 g	sodium chloride
0.055 g	calcium chloride
0.102 g	magnesium chloride

Add distilled water to 1000 ml; adjust to pH 7.2-7.3.

*Resin composition:

30 g	araldite CY212	resin
25.2 g	dodecanyl succinic anhydride (DDSA)	hardener
1.2 ml	2,4,6-tri-dimethylaminomethyl phenol (DMP 30)	accelerator
1.0 ml	di-butyl phthalate	plasticiser

Processed samples were embedded in resin filled silicone moulds and left to polymerise overnight at 60°C.

4.4 STAINING PROTOCOLS & STAINS

4.4.1 Haematoxylin and eosin (H & E) staining protocol

1)	xylene	2 mins
2)	absolute alcohol	2 mins
3)	methylated spirit	2 mins
4)	water	2 mins
5)	Lugol's iodine	1 mins
6)	water	1 min
7)	5% sodium thiosulphate	1 min
8)	water	
9)	Mayer's haematoxylin†	10 mins
10)	1% acid alcohol	3 dips
11)	water	2 mins
12)	Scot's tap water substitute‡	1 min
13)	water	2 mins
14)	methylated spirit	10 secs
15)	saturated alcoholic eosin	2 mins
16)	methylated spirit	2 mins
17)	absolute alcohol	2 mins
18)	histoclear	2 mins
19)	xylene	5 mins

† Mayer's haematoxylin:

1.0 g	haematoxylin
10.0 g	potassium alum
0.2 g	sodium iodate

Make up in 1 litre distilled water. Bring to boiling point and allow to cool overnight and add: 1.0 g citric acid and 50 g chloral hydrate.

‡ Scot's tap water:

3.5 g	sodium bicarbonate
20.0 g	magnesium sulphate

Make up in 1 litre of distilled water.

4.4.2 Cresyl violet staining protocol

1) Immerse sections to water
2) Preheated 0.1% acidified cresyl violet solutions for 6 mins. Wash briefly in water.
3) Differentiate in methylated spirit with acetic acid until nearly clear/ pale.
4) Dehydrate, clean, mount

4.4.3 Methylene blue/ azure II

1% methylene blue

1% azure II

1% borax

Make up in distilled water

4.4.4 Staining of tissues for electron-microscopy

1)	saturated uranyl acetate in 50% ethanol	5-15 mins
2)	50% ethanol	rinse
3)	50% ethanol	rinse
4)	distilled water	rinse x 2
5)	air dry	
6)	Reynold's lead citrate* (sodium hydroxide moistened chamber)	5-10 mins
7)	1 M sodium hydroxide	rinse x 3
8)	distilled water	rinse x 5

*Reynold's lead citrate:

1.33 g lead nitrate
1.76 g sodium citrate

Each dissolved in 15 ml distilled water for 1 minute, vigorous shaking followed by occasional shaking for the next 30 minutes. Clear with 8.0 ml 1 M sodium hydroxide and make up to final volume of 50 ml with distilled water (final pH 12).

4.5 IMMUNOCYTOCHEMISTRY

4.5.1 Hydration of the paraffin wax embedded tissue sections:

1)	xylene	2 mins
2)	absolute alcohol	2 mins
3)	methylated spirit	2 mins
4)	water	2 mins
5)	Lugol's iodine	1 min
6)	water	1 min
7)	5% sodium thiosulphate (hypo)	1 min
8)	water	

4.5.2 Peroxidase anti-peroxidase (PAP) immunostaining technique:

	Procedure	**Time & Temperature**	**Purpose**
1)	Immerse slides in 3 % hydrogen peroxidase (in absolute alcohol)	30 mins	Quench endogenous peroxidase activity
2)	Wash in running water	30 mins	
3)	Incubate in 10 % normal goat serum (NGS) in PBS*	2 hrs at room temperature (RT)	Block non-specific binding
4)	Incubate sections in the primary antibody in 1 % NGS in PBS	overnight at 4°C	
5)	Adjust sections to RT		
6)	Wash in PBS (6 changes)	30 mins	
7)	Wash in link antibody in 1% NGS	1 hour at RT	
8)	Wash in PBS (6 changes)	30 mins	Remove excess antibody
9)	Incubate sections in PAP complex	30 mins at RT	
10)	Wash in PBS (6 changes)	30 mins	Remove excess PAP complex
11)	Develop chromogen† until the required colour intensity had been achieved	30 secs to 5 mins	
12)	Wash sections in running water, dehydrated and mounted on DPX (BDH)		

*Phosphate Buffered Saline (PBS):

8 g	sodium chloride
0.2 g	potassium chloride
1.44 g	di-sodium hydrogen phosphate
0.2 g	potassium hydrogen phosphate

Dissolve in 800 ml distilled water, adjust pH to 7.4 with hydrochloric acid and make up to 1 litre with distilled water.

The chromogen was developed in filtered 0.1 M phosphate buffer (pH 7.3) containing 0.5 mg/ml 3,4,4',4',-tetraminobiphenyl hydrochloride (DAB) and 0.003 % hydrogen peroxide.

4.5.3 Protocol for PrP immunocytochemistry:

1) 5 μm sections floated on to Vectabond-coated slides
2) Sections to water
3) Picric acid 15 min
4) Water
5) 3 % hydrogen peroxide 30 min
6) Water
7) Hydrated autoclaving (121 °C for 10 min in distilled water)
8) Water
9) 96 % formic acid for 5 min
10) Water
11) 4M guanidine thiocyanate for 2 hours at 4 °C
12) Water then Tris buffered saline
13) Blocking serum for 20 min
14) Exposure to primary PrP antibody (3F4)
15) Tris buffered saline
16) Exposure to secondary antibody
17) Tris buffered saline
18) ABC kit
19) Tris buffered saline
20) Visualising agent
21) Water
22) Haematoxylin counterstain
23) Dehydration, clearing and mount in Pertex

24) Dried, mounted slides may be decontaminated again by immersion in 96 % formic acid for 5 min before labelling. This is regarding as a useful additional precaution as the slides leave a possibly contaminated laboratory.

Table 10. Antibodies, dilutions, links and sources used in PAP immunostaining.

Primary antibody	Dilution	Source	Link*	PAP complex	Source
rabbit anti-GFAP (bovine) (polyclonal)	1:1000 1:1500 1:2000 1:4000	DAKO	goat-anti rabbit (1:10)	rabbit (1:40)	ICN
mouse anti-SMI-31 (monoclonal)	1:1500 1:3000 1:4000 1:5000	Affinity Research Products	goat-anti mouse (1:10)	mouse (1:1250)	Sigma
α-Calbindin-D-28K	1:200	Sigma	goat-anti mouse (1:10)	mouse (1:1250)	Sigma

*All link antibodies were sourced from Sigma.

SECTION V.

REFERENCES

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