Chronic Canine Distemper Virus Encephalitis in Mature Dogs

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Abstract. Five dogs 2 to 8 years old with old dog encephalitis were compared to five other dogs, 4 to 8½ years old, with prolonged multifocal demyelinating distemper encephalitis. The dogs with old dog encephalitis had a diffuse panencephalitis involving most areas of the central nervous system with relative sparing of the cerebellum. The clinical signs were related to the cortical and subcortical lesions. The other dogs had severe focal necrotizing lesions mostly in the cerebellum and in the vicinity of the fourth ventricle; clinical signs were related to brainstem and spinal cord lesions. Viral isolation attempts were unsuccessful in the dogs with old dog encephalitis. In two dogs with multifocal encephalitis, canine distemper virus was isolated in tissue culture. The differences in lesions, clinical signs and observations in vitro indicate differences in pathogenesis between old dog encephalitis and multifocal demyelinating distemper encephalitis although both diseases may be caused by the same agent.

Subacute or chronic progressive panencephalitis in mature dogs has been reported since the beginning of this century [5, 6, 17, 18]. Different names were given to this condition but the most widely used term to date is “old dog encephalitis”. Canine distemper virus has been incriminated as the cause [14, 15] of old dog encephalitis and few cases have been reported in recent years [14, 15, 25]. Neurologic disease occurs frequently in puppies suffering from systemic canine distemper virus infection [8]. Neurologic signs may also occur in the absence of visceral or respiratory signs [8] and older dogs are also sometimes affected with this disease [8]. The brain lesions consist of multifocal areas of demyelination and necrosis of the white matter in certain predilection areas, particularly in the cerebellopontine area [8]. The relationship of this multifocal encephalitis to old dog encephalitis is not clear.

Materials and Methods

Ten mature dogs, 2 to 8½ years old, had progressive neurologic disorders. Each dog was given detailed physical and neurologic examinations [19]. Ancillary procedures included routine hematology and blood chemistry, cerebrospinal fluid examination (cell count, total protein, differential cytology), ophthalmoscopy and electroencephalography.

The central nervous system was removed at necropsy and fixed in 10% formol saline. After fixation, coronal blocks were cut at representative levels and processed for paraffin embedding.
Sections were cut at 4 micrometers and stained with hematoxylin and eosin (HE), luxol fast blue-cresyl echt violet and Holmes' silver impregnation. To demonstrate astroglial sclerosis, Holzer and PTAH stains were used on paraffin sections and Maurer's silver carbonate impregnation on frozen sections.

For fluorescent antibody testing blocks of brain tissue from parietal and frontal cortex, thalamus, pons, cerebellum and from medulla oblongata were obtained with sterile techniques at necropsy. Half the blocks were used for preparing tissue cultures, the other half for preparing impression smears and cryostat sections. Impression smears were made by applying a microscope slide to the cut surface of blocks of tissue. One part of the block was embedded for cryostat sectioning, quick frozen, and sectioned at 4 to 6 micrometers. Impression smears and cryostat sections were fixed in acetone at 4°C, rinsed in phosphate buffered saline and distilled water and then air dried. Cryostat sections from normal canine brain tissue were controls.

Fluorescein-labeled antisera against canine distemper virus were prepared in rabbits inoculated with an egg-adapted strain of canine distemper virus (Onderstepoort strain). The procedure for inoculation of the rabbits and labeling of the antisera has been described [13]. The sera were fractionated with 70% saturated ammonium sulfate, the globulin fraction was adjusted to 10 mg protein/ml in 0.2 mol/l phosphate buffer (pH 9.0) and the fluorescein isothiocyanate: protein ratio was 1:15. The optimal dilution and monospecificity of the fluorescent antibody preparation was determined as described [13].

The acetone fixed smears and cryostat sections from the infected and the normal dogs were stained with the fluorescein antisera preparation (diluted 1:4 in 0.025% Evans blue dye) for 30 minutes in a humidified chamber at 37°C. After staining, the sections were rinsed in phosphate buffered saline for 30 minutes, air dried and mounted with buffered glycerol (pH 7.2). Sections were examined with a fluorescent microscope equipped as described [13].

In six dogs the brain tissues from the above sites were prepared immediately after death for tissue culture. The tissues were minced in calcium- and magnesium-free Earle's balanced salt solution containing 0.25% trypsin. After trypsinization for 45 minutes at room temperature the cell suspension was centrifuged for 10 minutes at 800 rpm and resuspended in Eagle's minimal essential medium containing 20% fetal bovine serum, 200 units of penicillin, 200 micrograms of streptomycin, 2 micrograms of fungizone and 200 millimols of L-glutamine per milliliter. The brain cells were resuspended in a ratio of 1 milliliter of packed cells per 15 milliliter of Earle's minimal essential medium.

Primary lung macrophages were prepared from the infected dogs or from 4- to 6-week-old puppies as described [2] except that the cells were washed in Earle's balanced salt solution containing 0.25% trypsin. After trypsinization for 45 minutes at room temperature the cell suspension was centrifuged for 10 minutes at 800 rpm and resuspended in Eagle's minimal essential medium containing 20% fetal bovine serum, 200 units of penicillin, 200 micrograms of streptomycin, 2 micrograms of fungizone and 200 millimols of L-glutamine per milliliter. The brain cells were resuspended in a ratio of 1 milliliter of packed cells per 15 milliliter of Earle's minimal essential medium.

Confluent monolayers were trypsinized as above and the cell suspensions were adjusted to 1×10⁶ cells/ml.

For cocultivation 2 milliliters of the infected brain cells were mixed with 3 milliliters of cells of the different types (lung macrophages, trypsinized lung tissue cells, trypsinized dog kidney cells, VERO cells); the cells were seeded in 25-cm² sterile polypropylene tissue culture bottles. After 1 week or when confluent monolayers were obtained, the cultures were replenished with maintenance medium.

All cultures were examined daily by the fluorescent antibody technique for canine distemper virus cytopathogenic effects and weekly for presence of canine distemper virus.

As preparation for fluorescent antibody examination, the cells were trypsinized, suspended in 50 milliliters of Earle's balanced salt solution, and centrifuged at 800 rpm for 10 minutes. The supernatant was removed and the cells were resuspended in 0.2 milliliter of Earle's balanced salt solution. A drop of the suspension was placed on a microscope slide, allowed to air dry, and stained with the fluorescent antibody preparation as described above.
The primary cultures from four dogs (one dog with multifocal distemper encephalitis and three with old dog encephalitis) were subcultured after 4 weeks; at subculture the cultures were replenished with fresh primary dog cells. There were two to four passages at 4 week intervals. The VERO cells were subcultured every 2 weeks and with these cells nine passages were made.

Results

Clinical signs and neurologic data are outlined in tables I and II. All dogs were mature and there was no breed predisposition. Four dogs with old dog encephalitis were male. Incoordination and pelvic limb weakness were the predominant initial neurologic signs in dogs with multifocal distemper encephalitis whereas visual impairment was the common initial sign in dogs with old dog encephalitis. In most dogs in both groups, clinical signs had been present for at least 1 month before presentation, and in all dogs the signs had progressed. All dogs with old dog encephalitis were demented and tended to pace compulsively or circle. Most dogs in both groups had menace deficits with or without pupillary reflex abnormalities. Apart from nystagmus, brain stem signs of facial palsy, head tilt, head tremors and muscle atrophy were observed only in dogs with multifocal distemper encephalitis. Abnormal postural reactions and segmental spinal reflexes were recorded in both groups.

Systemic signs of distemper virus infection were not noted in any dog. Dog 2 had had a history of systemic distemper infection with chorea 6 years previously. Dogs 8 and 9 had recurrent generalized convulsions 2 and 4 years ago, respectively; neurologic signs remained static in dog 9 for 3 months after the initial presentation.

Dog 1 had 27 white blood cells/mm$^3$, predominantly lymphocytes, monocytes and macrophages, in the cerebrospinal fluid. A mononuclear pleocytosis that ranged from 10 to 70 white blood cells/mm$^3$ was found in four dogs with multifocal distemper encephalitis. Electroencephalographic abnormalities of slow wave, medium voltage activity were recorded in dogs 3, 4 and 5 with old dog encephalitis. Generalized lead hypersynchrony was found in dogs 8 and 9. Chorioretinitis was in dog 1 with old dog encephalitis. Dogs 6 and 10 with multifocal distemper encephalitis had retinal atrophy and subretinal exudative lesions, respectively. Fluorescent antibody tests on conjunctival smears for canine distemper virus was positive in dog 4 with old dog encephalitis. All dogs had normal hematologic and blood chemistry values.

No significant macroscopic lesions were found at necropsy.

In dogs 1, 2 and 5 there were diffuse changes throughout all divisions of the cerebral cortex. These changes were disseminated perivascular infiltration with lymphocytes and plasma cells, marked diffuse microglial proliferation and varying degrees of neuronal degeneration (fig. 1). Similar but more severe changes were throughout the basal ganglia, thalamus, hypothalamus and midbrain. In the latter areas there was a diffuse hypercellularity caused by increased numbers of microglial cells and, to a lesser degree, astrocytes. Neuronal degeneration was conspicuous and was often accompanied by neuronophagia. Perivascular mononuclear inflammatory cells often infiltrated the nervous parenchyma. The lesions were most severe in the pontine nuclei where there was widespread neuronal degeneration, nerve cell loss.
Table 1. Clinical data of dogs with old dog encephalitis

<table>
<thead>
<tr>
<th>Breed</th>
<th>Sex</th>
<th>Age, years</th>
<th>Initial neurologic sign(s)</th>
<th>Duration of sign(s) before presentation, days</th>
<th>Mental status</th>
<th>Locomotion</th>
<th>Cranial nerve function</th>
<th>Postural reactions</th>
<th>Spinal reflexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog 1</td>
<td>Mixed</td>
<td>6</td>
<td>Pelvic limb weakness</td>
<td>40 (43)</td>
<td>Depressed</td>
<td>Tetraparetic, stumbles into objects, occasional falling</td>
<td>Menace deficit bilaterally (pupillary reflexes intact)</td>
<td>Depressed in all limbs</td>
<td>Exaggerated in all limbs</td>
</tr>
<tr>
<td>Dog 2</td>
<td>Dachshund</td>
<td>Male</td>
<td>Visual impairment, head pressing</td>
<td>21 (23)</td>
<td>Depressed</td>
<td>Hyperkinetic, generalized hypermetria</td>
<td>Menace response and pupillary reflexes depressed bilaterally, vertical nystagmus</td>
<td>Depressed in all limbs</td>
<td>Exaggerated in all limbs</td>
</tr>
<tr>
<td>Dog 3</td>
<td>Mixed</td>
<td>7</td>
<td>Personality change; visual impairment</td>
<td>30 (33)</td>
<td>Depressed</td>
<td>Compulsive circling to the right</td>
<td>Menace deficit bilaterally (pupillary reflexes intact)</td>
<td>Depressed in left pelvic and pectoral limbs</td>
<td>Exaggerated in all limbs</td>
</tr>
<tr>
<td>Dog 4</td>
<td>Chow-Chow</td>
<td>Female (spayed)</td>
<td>Pelvic limb weakness, visual impairment</td>
<td>30 (60)</td>
<td>Extremely depressed</td>
<td>Tetraplegia</td>
<td>Menace deficit bilaterally, pupillary miosis, nystagmus</td>
<td>Depressed in all limbs</td>
<td>Exaggerated in all limbs</td>
</tr>
<tr>
<td>Dog 5</td>
<td>Mixed</td>
<td>2</td>
<td>Visual impairment</td>
<td>21 (27)</td>
<td>Depressed</td>
<td>Hyperkinetic, generalized incoordination</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

Numbers in parenthesis are duration of signs before dog was killed.
<table>
<thead>
<tr>
<th>Breed</th>
<th>Dog 6</th>
<th>Dog 7</th>
<th>Dog 8</th>
<th>Dog 9</th>
<th>Dog 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Bulldog</td>
<td>Yorkshire Terrier</td>
<td>Miniature Poodle</td>
<td>Chihuahua</td>
<td>Mixed</td>
</tr>
<tr>
<td>Age, years</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Initial neurologic sign(s)</td>
<td>4</td>
<td>5</td>
<td>8½</td>
<td>4</td>
<td>6½</td>
</tr>
<tr>
<td>Duration of signs before presentation, days</td>
<td>30 (42)</td>
<td>360 (363)</td>
<td>60 (90)</td>
<td>30 (120)</td>
<td>70 (73)</td>
</tr>
<tr>
<td>Mental status</td>
<td>Alert</td>
<td>Alert</td>
<td>Alert</td>
<td>Alert</td>
<td>Alert</td>
</tr>
<tr>
<td>Locomotion</td>
<td>Tetraplegic</td>
<td>Pelvic limb weakness</td>
<td>Generalized incoordination, spasticity of left sides limbs</td>
<td>Generalized incoordination, pelvic limb weakness</td>
<td>Generalized incoordination, pelvic limb weakness</td>
</tr>
<tr>
<td>Cranial nerve function</td>
<td>Menace response and direct pupillary reflex depressed left eye</td>
<td>Menace response and pupillary reflexes (direct/consensive) depressed bilaterally, right side facial palsy</td>
<td>Normal</td>
<td>Menace deficit in right eye, right side facial palsy and head tilt</td>
<td>Menace deficit bilaterally, head tilt to left, nystagmus, head tremors, temporalis and masseter muscle atrophy</td>
</tr>
<tr>
<td>Postural reactions</td>
<td>Depressed in all limbs</td>
<td>Depressed in pelvic and pectoral limbs</td>
<td>Depressed in left pelvic and pectoral limbs</td>
<td>Depressed in all limbs</td>
<td>Depressed in all limbs</td>
</tr>
<tr>
<td>Spinal reflexes</td>
<td>Exaggerated in all limbs</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Exaggerated in all limbs</td>
</tr>
</tbody>
</table>

1 Numbers in parenthesis are duration of signs before dog was killed.
and massive gliosis. There were also gliosis and spongy degeneration of the superior olivary nuclei and surrounding tissues. There was only mild involvement of the central cerebellar nuclei and none in the cerebellar cortex. In dog 5 the diffuse inflammatory process extended throughout the lower brain stem. In dogs 2 and 5 there was little involvement of the lower brain stem. The lesions in the white matter in dogs 1, 2 and 5 were much less dramatic, consisting of mild diffuse demyelination in the subcortical white matter. In dog 5 there was a large area of severe demyelination in the capsula interna and medial part of the cerebral peduncle. In all three dogs there was marked diffuse demyelination in the pontine area and middle cerebellar peduncles. Cowdry type A inclusion bodies were found in the cytoplasm and nuclei of neurons and glial cells in all three dogs (fig. 2). In dogs 3 and 4 there were extremely severe necrotizing changes throughout the frontal, parietal and occipital cortex, including the caudal parts of the hippocampus. In these areas there were varying degrees of diffuse neuronal loss and degeneration with replacement of the cortical tissue by vast numbers of large plump fibrillary astrocytes (fig. 3). There were also moderate to marked disseminated perivascular mononuclear cuffing and microglial proliferation. The lesions in the temporal lobes in both dogs were much milder, consisting of perivascular cuffs and diffuse microgliosis. Severe diffuse degenerative and sclerosing changes were also throughout the basal ganglia, diencephalon, midbrain and lower brain stem in dog 4. In dog 3 the severe grey matter sclerosing changes were restricted to the cerebral cortex; however, widespread neuronal degeneration and nerve cell loss were in the basal nuclei, thalamus and midbrain. Such changes were accompanied by perivascular cuffing and diffuse microgliosis. The lower brain stem was almost spared. The cerebellar cortex was relatively spared in both cases. White matter changes were severe in both dogs. There was marked diffuse demyelination throughout the cerebral white matter, especially in the corpus callosum, corona radiata, capsula interna and subcortical white matter of the frontal, parietal and occipital lobe (fig. 4a). There was only patchy involvement of the optic tracts. The demyelination of the cerebral white matter was accompanied by marked isomorphic gliosis (fig. 4b). In dog 4 there was also diffuse degeneration of the white matter throughout most of the brain stem. Myelin changes were mild in the cerebellum of both dogs. Intranuclear and intracytoplasmic Cowdry type A inclusion bodies were found in neurons and in astrocytes in both dogs.

In the dogs with multifocal distemper encephalitis there were multifocal necrotizing lesions in the cerebellopontine angle adjacent to the fourth ventricle, in the cerebellar and cerebral peduncles, the cerebellar white matter and in the optic tracts (fig. 5). In dogs 6, 8 and 10 the lesions had a cystic appearance with complete loss of the original architecture and strong gemistocytic and fibrillary astrogliosis. In dog 7 the focal lesions consisted of solid glial tissue (fig. 6). In dog 9 there was a marked diffuse astrogliosis in a large area of the medulla bordering the fourth ventricle but without massive loss of myelin or neurons. Thick perivascular mononuclear cuffs were associated with the focal lesions in dogs 6, 9 and 10 (fig. 5). In the cerebrum of dogs 6 and 8 several small plaque-like lesions were seen in the capsula interna and corona.
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Fig. 1: Cerebral cortex. Perivascular cuffing. Diffuse gliosis and nerve cell loss. HE.

Fig. 2: Cerebral cortex. Several intranuclear inclusion bodies (arrows) HE.

Fig. 3: Cerebral cortex. Massive fibrillary astrogliosis. Frozen section. Maurer’s stain for astrocytes.

Fig. 4: a. Cerebrum. Diffuse demyelination in subcortical white, corona radiata, corpus callosum and capsula interna. b. Same area. Marked astroglial sclerosis corresponding with demyelination. Holzer’s stain for astrocytes.

radiata. In these plaques there was demyelination with preservation of axons and marked astrocytic sclerosis. Such plaques were also associated with perivascular mononuclear cuffs. In dog 3 there was a large area of moderate diffuse demyelination with gliosis in the corona radiata and capsula interna on one side. In none of the dogs with multifocal distemper encephalitis were there lesions in the cerebral cortex. In all dogs inclusion bodies were found rarely and usually were located within astrocytic nuclei.

The results of the fluorescent antibody test are summarized in table III. In dogs 2, 3 and 5 with old dog encephalitis diffuse fluorescence was found in cryostat sections of the cerebrum, basal nuclei, thalamus, cerebellum and medulla. Canine distemper virus antigen was in neurons, their processes, glial cells and as coarse granular material without apparent cell association. The fluorescence was much less in white matter. There was no fluorescence associated with the perivascular cuffs.

In dog 10 with multifocal distemper encephalitis cytoplasmic fluorescence was observed in many cells in smears from the basal nuclei and rostral medulla. In dog
4 patchy areas of fluorescence were found on smears of the parietal cortex, thalamus and cerebellum. It was mainly confined to the cytoplasm, nuclei and processes of neurons. Less fluorescent material was present in glial cells.

Results of the tissue culture studies are tabulated in Table III. Viral isolation attempts from the brains of dogs 2, 3 and 5 with old dog encephalitis and dog 7 with multifocal distemper encephalitis were unsuccessful both with the primary brain tissue culture and the cocultivation technique. Canine distemper virus was successfully isolated from two dogs with multifocal distemper encephalitis. In all tissue cultures of dog 9, round fused cells were noticed 2 weeks after initiation of the cultures. These changes did not progress to destruction of the cell sheath but large syncytia were formed which remained constant for 5 weeks. Five weeks after initiation of the cell culture 30 to 40% of all cells had distemper virus as demonstrated by fluorescent antibody testing. The original cultures were subpassaged and observed for 4 additional weeks. A cytopathic effect as described occurred in these subcultures after 2 weeks.

Cytopathic effect typical for distemper was seen 3 weeks after inoculation of the tissue cultures from dog 10. Replication of canine distemper virus was confirmed by demonstration of positive immunofluorescence of the cultured cells. The cytopathic effect progressed slowly with formation of large syncytia.

Fig. 5: Focal lesion in vicinity of IV ventricle. Perivascular cuffing. Luxol fast blue-cresyl echt violet.

Fig. 6: Medulla oblongata. Edge of inactive lesion. Massive isomorphic gliosis (bottom) surrounded by perivascular cuffs. HE.
Discussion

Five dogs had slowly progressing neurological signs and had a diffuse active panencephalitis involving most parts of the brain with relative sparing of the cerebellum. These findings are consistent with a disease entity in the dog, described under various names such as disseminated encephalomyelitis in mature dogs [6], old dog encephalitis [14, 15], subacute diffuse sclerosing encephalitis [10, 24] and chronic dementional distemper [7]. According to previous reports [1, 5-7, 14-18, 20, 24, 25] this neurologic disease occurs mostly in middle aged dogs and is clinically characterized by slowly progressive neurologic signs, often including severe mental deterioration. The descriptions of the lesions consistently include diffuse gliosis and perivascular mononuclear cuffs throughout the cerebral cortex and brain stem with sparing of the cerebellum and absence of focal necrotizing lesions. Depending on the report, the white matter involvement varied from mild [14] to marked diffuse demyelination with periaxial sclerosis [24]. In some cases there was also severe sclerosis of the grey matter [25].

The clinical, pathological and immunological similarities between old dog encephalitis and subacute sclerosing panencephalitis in man has been stressed by several investigators [14, 15, 24]. As pointed out previously [1, 14, 15, 24] old dog encephalitis would be a useful animal model for the study of chronic progressive paramyxovirus infections in the central nervous system of man. Because old dog encephalitis is rare, research can not rely on spontaneous cases only. Experimental production of the disease is necessary. Distemper encephalitis in puppies is probably the most common neurologic disease in dogs and has been produced successfully in the laboratory [12]. That mature dogs with such lesions and prolonged survival times would be a potential source for experimental old dog encephalitis is doubtful in view of our findings. The dogs in our study with multifocal distemper encephalitis had mostly inactive lesions undergoing intense scar formation. Although some dogs had survived with neurologic signs for several months, no evidence was found for progression and spread of the lesions toward diffuse involvement as in old dog encephalitis. It is also striking that the cerebellum, a prime target in multifocal distemper encephalitis [8],

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Table III. Results of fluorescent antibody test and tissue culture studies

<table>
<thead>
<tr>
<th>Dog number</th>
<th>Fluorescent antibody test</th>
<th>Primary brain culture</th>
<th>Cocultivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>9</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>ND¹</td>
<td>+</td>
</tr>
</tbody>
</table>

¹ ND = not done.
is mostly spared in old dog encephalitis. The nature of the lesions and topographic localization are distinct between old dog encephalitis and multifocal distemper encephalitis. Our study suggests that multifocal distemper encephalitis does not progress to old dog encephalitis.

Although fluorescent antibody, electron microscopic and serologic studies suggest canine distemper virus as the cause of old dog encephalitis [14, 15], differences in clinical signs and lesions between old dog encephalitis and multifocal distemper encephalitis indicate differences in pathogenesis. The consistent failure of several workers [6, 14, 15, 24] and ourselves to isolate the infectious agent or to transmit the disease experimentally in old dog encephalitis contrasts with the relative high success rate of such experiments with material from multifocal distemper encephalitis. This suggests a different virus-host cell interaction in the two entities. That there was no progression from multifocal distemper encephalitis to old dog encephalitis provides further argument for the pathogenetic separation of both entities.

There have been speculations about the pathogenesis of old dog encephalitis [1, 14, 15, 25]. Ideas on disease mechanisms in slow virus infections have been presented [23]. Although the infectious agent has been characterized in vitro, the pathogenesis of subacute sclerosing panencephalitis in man remains obscure; viral as well as immunologic factors or combinations of the two have been proposed [11].

The significance of perivascular mononuclear cuffs in three dogs with multifocal encephalitis of long term survival is uncertain. Earlier investigations have found that perivascular cuffs increase in intensity as the dog survives longer [4]. In experimental distemper encephalitis perivascular cuffs occurred late in the disease [12]. It is possible that the presence of inflammatory cells may reflect the continued presence of viral antigen in the brain. We isolated canine distemper virus from two of our dogs with multifocal distemper encephalitis.

It would be useful to produce old dog encephalitis experimentally by inoculation of tissues derived from dogs with old dog encephalitis into other animals, but attempts have been unsuccessful [6, 14, 15, 24]. Chances of success would be improved if the virus could be isolated first in vitro. The techniques of cultivation of brain cells with other cell lines, as used in the isolation of the subacute sclerosing panencephalitis agent [22], were unsuccessful even though large quantities of distemper antigen were seen in the brain tissue with the fluorescent antibody test. Even if an infectious form of old dog encephalitis virus could be inoculated in experimental dogs, it is uncertain that a chronic progressive subacute sclerosing panencephalitis-like encephalitis would be produced. Immunological studies in man have shown that specific immune system aberrations may be responsible for the occurrence of subacute sclerosing panencephalitis [3, 21]. The importance of histocompatibility antigens in neurologic diseases of suspected viral cause has been shown [9]. Systematic tissue typing in naturally occurring canine distemper virus-related neurologic disease may allow us to detect a certain line of dogs susceptible to old dog encephalitis. Inbreeding of such dogs could then provide a source of suitable experimental animals for old dog encephalitis. Alternatively, experimental modification of the immune response in dogs infected with canine distemper virus may be the most realistic route for research.
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Clinical data indicate that old dog encephalitis and multifocal distemper encephalitis cannot be differentiated by breed, sex, age or initial neurologic signs. While both entities have a progressive course, there is a tendency for multifocal distemper encephalitis to have a longer duration than old dog encephalitis before obtendency occurs. The progressive clinical deterioration observed in our dogs with old dog encephalitis is well recognized [1, 5–7, 10, 14–16, 20, 24, 25]. There is, however, no information available on the clinical course of multifocal distemper encephalitis in mature dogs. If the animals are treated symptomatically, the condition may stabilize; this happened in one of our dogs. Old dog encephalitis can be differentiated from multifocal distemper encephalitis by the development of cortical and subcortical signs that include mental depression, unresponsiveness to environment, personality changes, and obstinate progression (hyperkinesia, compulsive circling, head pressing). Visual impairment is common in both and results from peripheral or central involvement or both.

The low incidence of cortical/subcortical signs and predominance of spinal cord/posterior brain stem signs in our dogs with multifocal distemper encephalitis provide further grounds for differentiation from old dog encephalitis.

References


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