Cerebellar Vermian Hypoplasia in Dogs

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Abstract. Six dogs with cerebellar dysplasia, in which the cerebellar vermis was hypoplastic, are described. Clinical signs in these dogs were noted around 2 weeks of age and included ataxia, dysmetria, and intention tremors. A variable portion of the caudal cerebellar vermis was absent in each dog; portions of the cerebellar hemispheres and flocculus also were absent in some of them. Neurons in certain brain stem nuclei that project to the cerebellum were either chromatolytic or vacuolated. Cerebellar vermian hypoplasia of dogs is analogous to the Dandy-Walker syndrome of human beings.

Cerebellar hypoplasia associated with in utero viral infection has been described in cats, cattle, and pigs. Additional inherited syndromes of cerebellar hypoplasia occur in cattle, horses, and several breeds of dogs. In most of these infectious and inherited syndromes, the cerebellum is either grossly normal or symmetrically smaller than normal. On microscopic examination, there usually are reduced numbers of Purkinje cells or distortion of the cerebellar cortical architecture or both. There have been other sporadic reports of dogs, cattle, horses, and goats in which the cerebellum was either hypo- or aplastic. In some of these cases the vermis was involved primarily while remaining portions of the cerebellum were relatively normal on both gross and microscopic examination. An additional six dogs with cerebellar dysplasia, in which the cerebellar vermis was hypoplastic, are described here.

Materials and Methods

Three dogs were evaluated at the University of Georgia College of Veterinary Medicine and three at the North Carolina State University School of Veterinary Medicine. After a variable course of diagnostic tests, all dogs were killed with pentobarbital and routine necropsies were done. Brains were fixed in 10% buffered formalin, serially sectioned, cut at 5 to 6 μm, and stained with cresyl violet (CV) and hematoxylin and eosin (HE) alone, or with luxol fast blue (LFB). Sections from representative areas of the brain were studied microscopically. However, a complete study was precluded in some cases because remaining unprocessed brain tissue was no longer available.

Results

Clinical signs first were noted in each dog around 2 weeks of age, when it began to walk (Table 1). Signs of cerebellar disease, such as ataxia, dysmetria, and intention tremors, were most common. Some dogs also had signs typical of vestibular disease (circling, nystagmus), presumably because of flocculonodular lobe involvement. All signs usually remained static, except for minimal improvement thought to be due to compensation, until the dogs were killed between 2 and 32 weeks of age. Dog 2 had a similarly affected littermate that was unavailable for study; littermates of the other dogs were either normal or had died due to what were presumed to be unrelated causes. The mother of dog 2 had bitten the pup at 2 days of age, but this was of questionable etiologic significance. Potentially causative in utero or immediate-postnatal factors were not identified in the other dogs. Results of cerebrospinal fluid evaluation in four dogs, skull radiographs in two dogs, and electroencephalography in one dog were normal. There were no antibodies to the canine distemper virus in the cerebrospinal fluid of the only two dogs tested.

A variable portion of the caudal cerebellar vermis was absent in each dog (Figs. 1–4). The pyramis, uvula, and nodulus lobules were involved most commonly. Portions of the right cerebellar hemisphere and flocculus were also absent in dogs 3 and 6 (Fig. 2), the right flocculus was reduced in size in dog 4, and the cerebellar hemispheres were bilaterally reduced in size, with the right being more severely involved in dog 1 (Fig. 3). The defect created by the absence of these cerebellar structures in dogs 2 and 3 was overlaid by a fluid-filled cyst which appeared to communicate with the fourth ventricle (Fig. 4). The brains of all dogs, otherwise, appeared grossly normal, except in dog 2. This dog had hydrocephalus and a portion of the left frontal cortex was absent.

Remaining areas of the cerebellar cortex were relatively normal microscopically except for focal or scattered evidence of Purkinje cell central chromatolysis and simple atrophy. The cell bodies of some Purkinje
Table 1. Clinical and pathologic findings in six dogs with cerebellar vermian hypoplasia.

<table>
<thead>
<tr>
<th>Dog Number</th>
<th>Breed</th>
<th>Sex</th>
<th>Age When Killed (wk)</th>
<th>Clinical Signs</th>
<th>Gross Brain Lesions</th>
<th>Principal Microscopic Brain Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Mixed</td>
<td>M</td>
<td>7</td>
<td>Ataxia, head tremors</td>
<td>Caudal cerebellar vermis absent; cerebellar hemispheres reduced in size</td>
<td>Cerebellum: Purkinje cells—chromatolysis and simple atrophy; focal reduction of granule cells; axonal spheroids</td>
</tr>
<tr>
<td></td>
<td>Labrador F.RET.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*CON: Central chromatolysis, gliosis</td>
</tr>
<tr>
<td>2.</td>
<td>Labrador F.</td>
<td>F</td>
<td>2</td>
<td>Ataxia, circling</td>
<td>Caudal cerebellar vermis absent and associated defect contained fluid-filled cyst; dilated fourth ventricle; portion of left frontal cortex absent and associated defect contained fluid-filled cyst; dilated lateral ventricles</td>
<td>Cerebellum: Purkinje cells—scattered central chromatolysis, some contain amorphous material in cytoplasm</td>
</tr>
<tr>
<td></td>
<td>retriever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>†LRN: Central chromatolysis, gliosis</td>
</tr>
<tr>
<td>3.</td>
<td>Bull terrier</td>
<td>M</td>
<td>14</td>
<td>Ataxia, dysmetria, intension tremors</td>
<td>Portions of caudal cerebellar vermis, right cerebellar hemisphere, and right flocculus absent; defect caused by absence of these structures was overlaid by a thin membrane</td>
<td>Cerebellum: Purkinje cells—scattered central chromatolysis, some contain amorphous material in cytoplasm</td>
</tr>
<tr>
<td></td>
<td>Weimaraner</td>
<td>M</td>
<td>16</td>
<td>Ataxia, circling, positional nystagmus</td>
<td>Portions of caudal cerebellar vermis and right flocculus absent</td>
<td>CON: Central chromatolysis</td>
</tr>
<tr>
<td>4.</td>
<td>Dachshund</td>
<td>M</td>
<td>8</td>
<td>Ataxia, intention tremors, mild left hemiparesis</td>
<td>Caudal cerebellar vermis absent</td>
<td>CON: Central chromatolysis</td>
</tr>
<tr>
<td></td>
<td>Bull terrier</td>
<td>F</td>
<td>32</td>
<td>Ataxia, head tremors, dysmetria, mild right hemiparesis</td>
<td>Portions of caudal cerebellar vermis, right cerebellar hemisphere, and right flocculus absent</td>
<td>CON: Central chromatolysis</td>
</tr>
</tbody>
</table>

* CON = Caudal olivary nuclei.
† LRN = Lateral reticular nuclei.
‡ LVN = Lateral vestibular nuclei.
§ LCN = Lateral cuneate nuclei.
¶ DCN = Deep cerebellar nuclei.
cells in dogs 2 and 3 were distended with amorphous material. There were scattered axonal spheroids and focal reduction of granule cells in the cerebellar cortex of dog 1. The deep cerebellar nuclei were not distinct in most cases, probably because of anatomic distortion caused by the vermian and hemispheric lesions. Neurons in a midline cluster, thought to be the fastigial nucleus, were vacuolated in dog 5.

The midline cleft resulting from the vermian lesion was partially lined by ependyma in dogs 1 and 5. In each of these two cases, there was a thin band of tissue that appeared to be contiguous with the molecular cell layer and meninges adjacent to the cleft. This tissue was also lined by ependyma in dog 5 and was presumed to represent membrane that had overlaid the cleft (Fig. 5). Whether it was a portion of the caudal medullary velum could not be determined. Lateral apertures through which the fourth ventricle communicated with the subarachnoid space were evident microscopically in all dogs except dog 5. In this case, sections that would allow such a distinction to be made were not available.

Principal microscopic lesions were present in brain stem nuclei that project to the cerebellum. Changes were most pronounced in the caudal olivary and lateral reticular nuclei. The lateral cuneate and lateral vestibular nuclei were affected to a lesser degree. Neurons in these nuclei often were either chromatolytic (Fig. 6) or vacuolated (Fig. 7). Some chromatolytic cells appeared to be degenerating with associated gliosis and increased microglia (Fig. 8). The cerebellar peduncles, spinocerebellar tracts, and remaining portions of the brain were microscopically normal in each dog.

**Discussion**

In each dog, a variable portion of the caudal cerebellar vermis was absent. This lesion was thought to have resulted from hypoplasia since there was little evidence of degeneration of differentiated structures. That the vermis was primarily involved distinguishes this syndrome from other conditions in dogs in which the cerebellum is uniformly hypoplastic or absent. Similarly, the relatively mild microscopic changes in differentiated portions of the cerebellum in these dogs contrasts with the dramatic reduction in Purkinje cells seen in most forms of canine cerebellar hypoplasia. The condition described here was termed cerebellar vermian hypoplasia to emphasize these differences. However, one or both of the cerebellar hemispheres or the flocculus also were hypoplastic in four of the dogs.
Occasional dogs and goats with analogous cerebellar vermian lesions have been described. Hypoplasia of the caudal cerebellar vermis also occurs in human infants with the Dandy-Walker syndrome. Additional lesions seen in some human patients with this syndrome include hydrocephalus, cystic dilatation of the fourth ventricle, rostral displacement of remaining cranial portions of the vermis, enlargement of the caudal fossa, agenesis of the corpus callosum, and atresia of foramina of the fourth ventricle. Hydrocephalus was identified in dog 2 of this report and in three of the other reported cases. An additional 3-week-old, female Australian shepherd dog with vermian hypoplasia and hydrocephalus also
has been seen (R. A. LeCouteur, unpublished observations, 1985). Cysts within the caudal fossa were identified in only two of the dogs reported here; however, distortion of the meninges at the time of brain removal may have disrupted cysts in some dogs. Similar cysts were also present in two of the other reported canine cases. Additional anomalies seen in the Dandy-Walker syndrome were not seen in dogs of this report or in other reported canine cases of cerebellar vermian hypoplasia.

The etiology of the cerebellar lesions in infants with the Dandy-Walker syndrome and in dogs remains poorly defined. Several groups of siblings have been affected with the Dandy-Walker syndrome, suggesting a heritable basis in some cases. A simple autosomal recessive mode has been suggested. \^1^\(^2\), \^2\(^2\) Two of the previously reported dogs with primarily vermian hypoplasia were Boston terrier littermates, \^1\(^5\) and another dog with both vermian and hemispheric hypoplasia was a cross between a Boston terrier and a Manchester terrier, \^7\) suggesting there also may be a heritable basis in this breed. The owners of the dogs in this report knew of no related dogs with similar signs, except for the littermate of dog 2. Chemical teratogens have been considered in the pathogenesis of other cases of the Dandy-Walker syndrome since galactoflavins induces similar lesions in mice. \^2\(^3\) However, specific teratogens responsible for human cases have not been discovered, and there were no identifiable in utero or immediate postnatal teratogens in the dogs of this report or in those described by others.

Because of their morphologic similarities, cerebellar vermian hypoplasia of dogs and the Dandy-Walker syndrome may share pathogenetic mechanisms. Initial attempts to account for the occurrence of the Dandy-Walker syndrome focused on atresia of the foramina of Luschka and Magendie. \^2\(^4\) Resultant distension of the fourth ventricle with cerebrospinal fluid was presumed to interfere with differentiation of the caudal vermis from the metencephalic alar plates. This theory, though, was discounted by studies showing that the cerebellar vermis differentiates prior to the appearance of foramina within the fourth ventricle. \^7\) It is not surprising, therefore, that morphologically normal lateral recesses and apertures through which the fourth ventricle communicated with the subarachnoid space were evident microscopically in all five dogs of this report in which such a determination could be made. While a definitive alternate theory for the pathogenesis of the Dandy-Walker syndrome has not yet been proposed, most investigators still believe that distension of the embryonic fourth ventricle interferes with the formation of the cerebellar vermis. \^8\) The distension may occur because the primitive caudal medullary velum overlying the fourth ventricle in affected individuals is abnormally impermeable to cerebrospinal fluid. A similar lesion might lead to cerebellar vermian hypoplasia in dogs; however, we were unable to critically evaluate the caudal medullary velum in these dogs.

Microscopic changes in dogs of this report were most pronounced in neurons of brain stem nuclei with efferents that project to the cerebellum. Central chromatolysis and vacuolation occurred most commonly. Changes occurring in this manner represent retrograde transsynaptic neuronal degeneration since processes from the secondarily involved cells project towards the neurons with the primary lesion. Retrograde neuronal lesions similar to those seen here have been recognized in brain stem nuclei after a number of other spontaneous and experimental cerebellar lesions. After excision of various portions of the cerebellum, neurons in the caudal olivary, \^4\) lateral reticular, \^6\) and lateral cuneate \(^2\) nuclei undergo predominantly chromatolysis followed by degeneration in immature animals and simple atrophy in adults. Central chromatolysis has also been recognized in brain stem nuclei of cats with other forms of cerebellar hypoplasia \(^1\(^0\) and in the caudal olivary nuclei of dogs with Purkinje cell degeneration. \^2\(^6\)

Neuronal vacuolation (fenestration) occurs most commonly in human beings in association with anterograde transsynaptic neuronal degeneration, \^1\(^7\) particularly in the caudal olivary nuclei subsequent to dentate nuclei and central tegmental tract lesions. \(^9\), \(^2\(^3\) A similar mechanism may have been partially responsible for this lesion in these dogs since the deep cerebellar nuclei were poorly formed in some of them. However, because the neuronal vacuolation was present in multiple nuclei that project to the cerebellum, it seems more likely to be associated with the overall reduction in Purkinje cells. This is interesting in that neuronal vacuolation usually does not occur in human beings subsequent to retrograde transsynaptic degeneration. \(^1\(^7\), \(^2\(^0\) It has, however, been seen in the caudal olivary nuclei of dogs with Purkinje cell degeneration. \^1\(^3\)

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