

The Armed Forces Institute of Pathology
Department of Veterinary Pathology
WEDNESDAY SLIDE CONFERENCE
2004-2005

CONFERENCE 20
30 March 2005

Conference Moderator: Dr. Brian Summers, PhD, MRCVS, FRCPath, DACVP
Professor of Pathology
Department of Biomedical Sciences
Cornell University, College of Veterinary Medicine
Ithaca, New York

CASE I – 99-10725 (AFIP 2683903)

Signalment: 2-month-old, male, Arabian horse (*Equus caballus*).

History: This colt had a spastic gait, ataxia and head tremors for about two weeks prior to elective euthanasia.

Gross Pathology: No significant gross lesions were noted in the thoracic or abdominal viscera. The cerebrum and cerebellum appeared normal in size and development, externally. A sagittal section of the cerebellum revealed less prominent folia in the cranial and dorsal areas of the vermis.

Laboratory Results: A computerized tomography (CT) scan of the brain was inconclusive.

Contributor's Morphologic Diagnosis: Cerebellar cortical abiotrophy.

Contributor's Comment: The history and gross and microscopic lesions in this case are consistent with a diagnosis of cerebellar cortical abiotrophy. Affected animals are usually neurologically normal at birth with clinical signs developing at various times in postnatal development. Spasticity and ataxia are observed in the gait, especially in the forelimbs. Grossly, the cerebellar folia are best developed (or least degenerative) in the caudal and ventral areas of the cerebellum (see gross photograph). The cerebellum was not weighed in this case but in normal horses the cerebellum should be about 10-12% of total brain weight. Microscopically, there are degenerative and missing Purkinje cells with a reduction in all layers where Purkinje cells are absent. There is accentuation of radial astrocyte processes

in the molecular layer. The cause of this condition is unknown, although a hereditary component (autosomal recessive trait) is suspected.

AFIP Diagnosis: Brain, cerebellum: Purkinje and granular cell degeneration and loss (cerebellar cortical abiotrophy), diffuse, moderate, with mild Wallerian degeneration in the folia white matter, and mild gliosis of cerebellar nuclei, Arabian, equine.

Conference Comment: Conference attendees discussed the relationship between the normal development and physiology of the cerebellum and the clinical and histopathological changes identified in this case.

The term abiotrophy literally means the lack of a life-sustaining nutritive factor. Implicit in its use in veterinary medicine is the presumption that the premature neuronal degeneration is not an acquired insult, but rather the consequence of an intrinsic metabolic disorder. However, the specific metabolic derangement may vary from syndrome to syndrome. The hallmark of cerebellar abiotrophic diseases is the premature demise of discrete and often functionally related populations of neurons, after the organ has developed its full cellular complement.¹

In abiotrophic conditions encountered in veterinary medicine, neurological deficits usually begin in the first few weeks to months of life, are progressive, and are inherited in studied populations. The clinical hallmark of cerebellar cortical abiotrophies is neurological normality at birth, followed by the development of cerebellar deficits that progressively worsen in the post-natal period. In contrast, in-utero damage, such as with viral agents that may damage the developing cerebellum at a very precise stage of fetal life, results in cerebellar ataxia from the time of birth. Because the injury is not ongoing, the neurological deficits are often static and may even slowly improve as the animal learns to compensate.¹

Microscopically, cerebellar cortical abiotrophies are characterized by ongoing neuronal degeneration and loss, with reactive gliosis in the background of a normally developed cerebellum. Neither folial dysplasia nor neuronal heterotopia occurs in cerebellar cortical abiotrophies; they are features of in-utero viral infections that can disrupt normal cerebellar development. Purkinje cells are usually affected first in abiotrophies, and, in general, a reduction of the granule cell neurons follows. There is often proliferation of astroglia (Bergmann astrocytes) in the affected folia and a mild gliosis of the molecular layer. Due to Purkinje cell degeneration, Wallerian degeneration may be found in the white matter of the folia and low numbers of spheroids may be present in the granular layer, cerebellar white matter, or the nuclei of the cerebellar medulla. Cerebellar nuclei are often gliotic.¹

Cerebellar abiotrophies have been reported in a number of domestic and laboratory species, including dogs, cattle, sheep, Yorkshire pigs and Arabian horses and Gotland ponies. The time of onset of clinical signs varies with the species and breed affected. Common dog breeds affected include Kerry Blue Terriers, Gordon Setters and Rough-Coated Collies. Veterinary Neuropathology provides a more thorough list of predisposed breeds.¹ The syndrome in Kerry Blue Terriers is unique since the caudate nucleus and the substantia nigra are also affected. Cerebellar abiotrophy of Gordon Setters is unusual since it has a delayed onset, with clinical signs not typically appearing until six to 24 months of age. Kerry Blue Terriers and Rough-Coated Collies may have extracerebellar involvement, with Wallerian degeneration in the brainstem and spinal cord.

Contributor: University of Minnesota, College of Veterinary Medicine, Veterinary Diagnostic Laboratory, 1333 Gortner Avenue, St. Paul, MN

References:

1. Summers BA, Cummings JF, de Lahunta A: Veterinary neuropathology, pp. 300-305. Mosby, St. Louis, MO, 1995
2. Palmer JD, Blakemore WF, Cook WR, et al: Cerebellar hypoplasia and degeneration in the young Arab horse: clinical and neuropathological features. Vet Rec **93**:62-66, 1973
3. Baird JD, MacKenzie CD: Cerebellar hypoplasia and degeneration in part-Arab horses. Aust Vet J **50**:25-28, 1974
4. Sustronck B, Mylle E, De Geest J, De Smidt M: Cerebellaire abiotrofie bij drie arabische volbloedveulens. Vlaams Dier Tijd **59**:151-154, 1990

CASE II – 51304 (AFIP 2947490)

Signalment: 14-year-old, male-castrated, Golden retriever.

History: In early spring 2003, the dog began to become bilaterally paretic in the rear legs. This progressively got worse. In November 2003, a cervical laminectomy was performed. The dog did not get any better following surgery. After six months, the owner opted for euthanasia.

Gross Pathology: No gross abnormalities were noted.

Contributor's Morphologic Diagnosis: Meninges: Pachymeningitis, ossifying, diffuse, severe with fibrosis.

Contributor's Comment: The case resembles closely a case described in the Journal of the American Veterinary Medical Association,¹ except that it is far more extensive, with involvement of the entire spinal cord. A comment on their report was written by Dr. John McGrath,² who felt that they had over-interpreted the lesion. The case and lesion are unusual, but the effects on the animal were severe, as are the lesions. A differential diagnosis that might be considered is Lyme disease.

AFIP Diagnoses: 1. Leptomeninges, spinal: Fibroplasia, diffuse, with vascular hyalinization, and multifocal arachnoid cell proliferation, Golden Retriever, canine.
2. Dura, spinal: Osseous metaplasia, focal.
3. Spinal cord, ventral funiculi: Axonal degeneration and loss, mild, with dilated myelin sheaths, axonophagia, and rare spheroids.

Conference Comment: There is significant variation in slides and not all features may be present on all slides. In the sections reviewed by conference attendees, the major histological changes in the arachnoid layer included fibroplasia, vascular hyalinization, and multifocal arachnoid cell proliferation. The osseous metaplasia noted in some slides is within the dura mater.

The literal definition of pachymeningitis is inflammation of the pachymeninges, also known as dura mater. Metaplastic ossification of the spinal dura occurs most frequently in the lumbar region of large and giant breed dogs, and is sometimes referred to as ossifying pachymeningitis. These grayish islands of lamellar bone may contain adipocytes and myeloid elements and are an incidental, age-related change. An association with intervertebral disk prolapse has been suggested, but this metaplastic change can be found in the cranial dura also. In addition, thickening (sclerosis) as a result of fibrosis, with acellular collagen deposition or hyalinization, may be found in the leptomeninges and choroid plexus stroma of old animals.³ Residents also noted small amounts of perivascular lipofuscin accumulation, particularly in the gray matter. This too is a common finding in older dogs.

Of additional interest in this case is the axonopathy in the ventral funiculi, which is likely due to focal or diffuse disease rostral to this segment and may be the cause of the clinical signs noted in this case. Nonetheless, the histopathological lesions in the spinal cord are likely not the result of the meningeal lesions. The causes of the leptomeningeal changes and the spinal cord axonopathy are not evident in the slides examined in conference.

Contributor: Johns Hopkins University School of Medicine, Department of Comparative Medicine, 733 North Broadway, Suite 811, Baltimore, MD

References:

1. Wilson J, Greene H, Leipold H: Osseous metaplasia of the spinal dura mater in a Great Dane. J of Am Vet Med Assoc **167**(1):75-7, 1975
2. McGrath JT. Letter: Spinal ossifying pachymeningitis. J of Am Vet Med Assoc **167**(12):1045-1048, 1975
3. Summers BA, Cummings JF, de Lahunta A: Veterinary neuropathology, pp. 52-53. Mosby, St. Louis, MO, 1995

CASE III – 03-1499 (AFIP2935569)

Signalment: 4-month-old, female mixed breed goat.

History: Recumbent for one week. The animal had some tremors and stiff hind limbs.

Gross Pathology: None.

Contributor's Morphologic Diagnoses: 1. Cerebellar abiotrophy.
2. Neuronal and axonal degeneration, spinal cord, mild.

Contributor's Comment: The cerebellar folia have depletion of the granular cell layer and loss of Purkinje cells. Chromatolysis is seen among the remaining Purkinje cells and in the large neurons within the brainstem. The spinal cord has mild Wallerian degeneration of the ventral white matter tracts and chromatolysis of neurons in the ventral horn. The cerebellar lesion is consistent with cerebellar abiotrophy, but when taken in consideration with the spinal cord lesions, this case is an example of a multisystem neuronal degeneration.

Multisystem neuronal degeneration is a degeneration or abiotrophy of neurons in multiple locations throughout the nervous system. In humans these include both familial and acquired conditions and may affect single or multiple neuronal systems, including motor, sensory and autonomic neurons. Neuronal system degenerations have been reported in a pig and several breeds of dogs, including the Swedish Lapland reindeer-herd dog, Cairn Terrier, Cocker Spaniel and Miniature Poodle. These primarily affect the brain and spinal cord and are inherited in all but the Miniature Poodle. Cerebellar abiotrophy and multisystem neuronal degeneration have not been reported in the goat.

AFIP Diagnoses: 1. Brain, cerebellum: Purkinje and granule cell degeneration and loss, diffuse, moderate, with Purkinje cell ectopia, and molecular gliosis, mixed breed, caprine.

2. Brainstem, medulla oblongata; spinal cord, ventral column: Neuronal degeneration (chromatolysis), multifocal, mild to moderate, with gliosis.

Conference Comment: In contrast to the first case, not only is there Purkinje cell degeneration and loss, but there is also Purkinje cell ectopia with moderate numbers of Purkinje cells located in the molecular layer. The latter indicates this degenerative disease began in-utero when the Purkinje cells were still migrating from the internal germinal layer adjacent to the fourth ventricle.²

The histopathological changes present in the cerebellum, brain stem, and the spinal cord, suggest copper deficiency as a possible etiology. Copper deficiency can cause two clinical neurologic disease syndromes in sheep and goats: congenital (swayback) and acquired (enzootic ataxia).

In the congenital form (swayback), the condition develops in-utero and clinical signs are present at birth with affected animals being totally recumbent or severely ataxic. Other signs include depression, head shaking, trembling, and most affected animals die soon after birth. Grossly, there may be small foci of gelatinous softening, or cavitation of the cerebral hemispheres. Microscopically there is absence or destruction of the white matter of the cerebral hemispheres with chromatolysis of large motor neurons of the red and vestibular nuclei. Demyelination of the motor tracts of the white matter of the spinal cord has also been reported.³

The delayed form (enzootic ataxia) develops after birth with animals appearing normal at birth and developing signs of the disease from one week to six months of age. Clinical signs include incoordination, ataxia, and posterior paresis. Lesions are limited to the large neurons of the brain stem and spinal cord. However, goats with enzootic ataxia may have well defined lesions in the cerebellum, including patchy cerebellar hypoplasia, necrosis, and loss of Purkinje cells and depletion of the granular cell layer.³

Swayback and enzootic ataxia may result from either primary or secondary copper deficiency. Primary copper deficiency is caused by a diet that is low in copper. Secondary copper deficiency results from dietary composition, which determines the proportion of dietary copper that is absorbed. It is well known that other minerals, such as molybdenum, sulfur, and iron can interfere with proper copper utilization. However, food type and the interaction between food type and mineral composition will also affect copper absorption and utilization.³

Contributor: Virginia Tech, College of Veterinary Medicine, Department of Biomedical Sciences & Pathobiology, Blacksburg, VA
www.vetmed.vt.edu

References:

1. Summers BA, Cummings JF, de Lahunta, A: Veterinary Neuropathology, pp. 300-307. Mosby, St. Louis, MO, 1995
2. De Lahunta A: Cerebellum. *In*: Veterinary Neuroanatomy and Clinical Neurology, 2nd ed., pp. 255-256. W.B. Saunders Company, Philadelphia, PA, 1983
3. Banton MI, Lozano-Alarcon F, Nicholson SS, Jowett PLH, Fletcher J, Olcott BM: Enzootic ataxia in Louisiana goat kids. J Vet Diagn Invest 2:70-73, 1990

CASE IV – TAMU 04-02 (AFIP 2941201)

Signalment: 10-day-old, male Brangus calf.

History: The calf was born in a pasture and found recumbent with a “hole in the back.” The calf never walked, and was brought into the clinic as a donation. At presentation, the animal was moribund and considered septicemic. He had a withdrawal reflex in all limbs but could not stand. A skin defect over a deep hole was noted on the dorsum in the thoraco-lumbar area. No work-up was conducted, and a clinical diagnosis of spina bifida preferred. The animal was euthanized.

Gross Pathology: Decubital ulcers were over bony prominences. A 2X1.5 cm, open, skin defect was at the T13-L1 junction. Another depression in dorsal, axial tissues was at the L6-S1 junction, but was not associated with a skin defect. The dorsal arch of the T13-L1 junction was absent and a hyalinized membrane connected the spinal canal to the “hole” seen grossly. The spinal cord became attenuated and deviated dorsally into the membrane. No spinal cord was seen from L1 to approximately L3 (spinal dysraphism in its broadest definition; segmental spinal cord aplasia or necrosis). The spinal column began again and continued normally from L4 caudally. A fibrous band was in the area of the arch at L6-S1, and the dura and spinal cord appeared normal in this area (spina bifida occulta).

The cortex of the occipital pole of the brain extended caudally over the cranial aspect of the cerebellar cortex at the midline with a redundant or hamartomatous growth of the marginal gyrus (local, cerebral-cortical dysplasia/redundancy). Meninges were slightly opacified. The lateral ventricles were twice normal volume (hydrocephalus)

Macroscopic Diagnosis: Multiple spina bifida aperta and occulta; spinal dysraphism/focal spinal cord aplasia/necrosis; meningitis, hydrocephalus, cerebral cortical hamartomatous dysplasia.

Contributor's Morphologic Diagnosis: Severe, subacute/chronic suppurative meningomyelitis, with granulation tissue and numerous bacteria; spinal meningocele; spinal dysraphism with agenesis of the spinal cord, OR absence of spinal cord, OR hypoplasia of the spinal cord, OR duplication of the spinal canal AND/OR diastematomyelia

Contributor's Comment: Malformations offer special challenges to the diagnostician. The most important decision is determining if the malformations are hereditary. I do not believe this is a hereditary condition. The low incidence of such lesions and the inadequate histories in our necropsy population usually make that determination impossible. The variation in malformations between individuals makes comparison between cases of malformations difficult, and usually, the diagnosis is a descriptive exercise.^{1,2,3,5,7,8,12,13} Often, one malformation is accompanied by or leads to more malformations. Sometimes, names given to cases are inaccurate. Depending on the level of the section received, the lesion you see on your slide will vary in this presented case. A unifying theme is subacute to chronic inflammation with granulation tissue, neutrophilic and histiocytic exudates, and bacteria associated with fibrin and necrosis. An occasional thrombus is noted (considered a consequence not a primary lesion). The animal could not move and history suggested the animal's back lesion (the myelocele) had been pecked at by birds. Thus, with the opening to the CNS, sepsis became rampant in this case (and other similar cases in our files). The meninges surround the cord as the cord 1) moves dorsally, 2) becomes smaller, 3) loses its central canal, 4) is progressively bisected to give diastematomyelia, 5) becomes a small core of nondescript neural tissue, and then, 6) disappears from the section.

A series of images is provided for all participants to follow. The entire affected area of cord was blocked and cut.

Figure 4. Cranial to the meningocele (2X).

Figure 5. Cord at start of the "coele" (2X).

Figure 6. Cord with ventral fibrous septum dissecting the cord (2X).

Figure 7. Fibrous septum dividing the cord (diastematomyelia) (2X).

Figure 8a. Fibrous tissue and remnant neural parenchyma (2X).

Figure 8b. Remnant neural tissue of 8a, note thrombus (10X)

Figure 9. Intact cord with two central canals distal to the meningocele (2X).

The sections where spinal cord is not present are not submitted. One could argue that the infection destroyed the cord in this area; however, the progressive diminution of tissue and persistence of remnant cord in caudal sections of the affected area as described above argues against this theory. Segmental loss of spinal cord with reappearance in both cervical and lumbo-sacral areas is described in calves.^{5,7,10,11} Such segmental loss in areas where the development of a canal and mesenchymal structures is complete suggests to me that the cord was present at one time to allow induction of somite development, and only later, the cord underwent necrosis. Subsequently, the lumbar and sacral cord reappears as normal except for a brief caudal lumbar segment with duplication of the central canal and the continued inflammatory change seen at all levels of the cord and brain. The loss of the dorsal bony arch in the lumbo-sacral junction was associated with no defect in the associated cord and is spina bifida occulta. The withdrawal reflex noted clinically is a spinal reflex and not demonstrative of perception of deep pain. It is tempting to say that the premature termination of the cord with its filamentous end not going into the meningocele may represent tethering of the cord.

Spina bifida is a form of rachischisis/cleft vertebral canal.^{4,6,14} Dysraphism is failure of a fusion of a raphe. Interestingly, the term per se is not defined in or not even used by some current human neuropathology texts. However, some authors³ have (incorrectly I believe) used the term more broadly to include any "myelodysplasia" including: aplasia, hydromyelia, syringomyelia, fusion failures of the neural tube, etc.. Unfortunately, I was taught and remember that Weimaraner dogs had a condition of spinal dysraphism, which is an incorrect diagnosis for the condition.¹⁵ It is syringomyelia, hydromyelia, and central canal dysplasia. I think the term, dysraphism, should be used generically when there is a neural tube fusion disorder. Most cases of spina bifida have a closed neural tube. We will not discuss the process of closure of the neural tube (Chapter 8 in Greenfield's), but it occurs as a bidirectional process occurring multifocally in both the spinal cord and brain. The caudal spinal cord develops by secondary neurulation via a growth of neural cells caudally, NOT from a tube. The lumbosacral spina bifida occulta of this case is probably the result of a defect in this secondary neurulation process. Spina bifida's pathogenesis is thought to involve: 1) abnormal proliferation of neural tissue in this area, 2) focal ischemic injury, or 3) an idiopathic/undefined maldevelopment of the tail bud.

Spinal cord anomalies often are associated with brain malformations, especially Chiari II malformations; however, the cerebellar vermis in this animal is normal. The redundant cortex seen is not part of a described syndrome. Hydrocephalus is common in cases of spina bifida as well.

AFIP Diagnosis: Spinal cord: Myelodysplasia, severe, with duplication of spinal roots, chronic suppurative meningitis, granulation tissue, and numerous bacteria, Brangus, bovine.

Conference Comment: The contributor provides an excellent description, possible pathogenesis, and discussion of the lesions present in this case. There is considerable variation in slides and not all lesions described may be present on all slides.

Spina bifida in its customary usage refers to absence of the dorsal portions of the vertebrae. It is an imperfect name as the various forms of the defect largely represent differences in the degree of defective closure of the neural tube, its separation from the ectoderm, and its induction of a skeletal investment. Often, the defect is divided into several classes on the basis of severity. Myeloschisis, spina bifida occulta, spina bifida cystica with meningocele, and spina bifida with myelomeningocele apply to the vertebral defect. Amyelia, diastematomyelia, hydromyelia, and dysraphism apply to the spinal cord defect. The most severe forms of myelodysplasia occur in association with spina bifida, as seen in this case.¹⁵

Contributor: Texas A&M University, College of Veterinary Medicine, Department of Veterinary Pathobiology, College Station TX
<http://vtpb-www.cvm.tamu.edu/>

References:

1. Bradley R, Kirby FD: Anomalous development of the spinal cord in a calf. *Vet Pathol* **16**:49-59, 1979
2. Cho DY, Leipold HW: Arnold-Chiari malformation and associated anomalies in calves. *Acta Neuropath* **39**:129-133, 1977
3. Cho DY, Leipold HW: Spina bifida and spinal dysraphism in calves. *Zbl Vet Med Assoc* **24**:680-695, 1977
4. Davis RL, Robertson DM: *Textbook of Neuropathology*, 3rd ed. Williams & Wilkins, Baltimore, MD, 1997
5. Doige CE: Spina bifida in a calf. *Can Vet Jour* **16**:22-25, 1975
6. Graham DI and Lantos PL: *Greenfield's Neuropathology*, Vol. 1, 6th ed. Arnold, London, England 1997
7. Goss, LJ and Hull FE: Spina bifida in a calf. *Cornell Vet* **29**:239-240, 1939
8. Gruys E: Dicephalus, spina bifida, Arnold-Chiari malformation and duplication of thoracic organs in a calf. *Zbl Vet Med Assoc* **20**:789-800, 1973
9. Leipold HW, Cates WF, Radostits OM, Howell WE: Spinal dysraphism, arthrogyposis and cleft palate in newborn Charolais calves. *Can Vet Jour* **10**:268-273, 1969

10. Leipold HW, Cates WF, Radostits OM, and Howell WE: Arthrogryposis and associated defects in newborn calves. *Am J Vet Res* **31**:1367-1374, 1970
11. Madarame H, Azuma K, Nozuki H, and Konno S: Perocormus associated with segmental aplasia of the cervical spinal cord in a Japanese shorthorn calf. *J Comp Path* **101**:225-230, 1989
12. Madarame, H, Ito, N, and Takai, S: Dicephalus, Arnold-Chiari malformation and spina bifida in a Japanese black calf. *J Vet Med Assoc* **40**:155-160, 1993
13. McFarland, LZ: Spina bifida with myelomeningocele in a calf. *J Am Vet Med Assoc* **134**:32-34, 1959
14. Summers BA, Cummings JF, and de Lahunta A: *Veterinary Neuropathology*. Mosby-Year Book, Inc., St. Louis, MO, 1995
15. Jubb KVF, Huxtable CR: The nervous system. *In: Pathology of Domestic Animals*, eds. Jubb KVF, Kennedy PC, Palmer N, 4th ed., vol. 1, pp. 273-274. Academic Press, San Diego, CA, 1993

Signature Authenticated by Approve
Approved by: Shelley P Honnold,
: Sunday, 17 April, 2005 at 14:14:

Shelley P. Honnold, DVM
Major, Veterinary Corps, U.S. Army
Wednesday Slide Conference Coordinator
Department of Veterinary Pathology
Armed Forces Institute of Pathology
Registry of Veterinary Pathology*

*Sponsored by the American Veterinary Medical Association, the American College of Veterinary Pathologists and the C. L. Davis Foundation.