PEER REVIEWED

A Review of Inherited Central Nervous System Dysfunction in Calves

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Abstract

Differentiating inherited central nervous system diseases in calves from non-inherited disorders is important due to significant ramifications to the herd breeding program and the poor prognosis associated with them.

Well documented and suspected inherited conditions that cause central nervous system (CNS) dysfunction in calves include progressive degenerative myeloencephalopathy, spinal muscular atrophy, degenerative axonopathy, spinal dysmyelination, citrullinemia, cerebellar abiotrophy, progressive ataxia, spastic paresis, maple syrup urine disease, neuraxial edema, bovine familial convulsions, storage diseases, neuronal lipodystrophy and myelodysplasias.

This review briefly describes the signalment and common clinical signs of many proven or presumably inherited conditions that cause CNS dysfunction in calves. These diseases are categorized by localization of the predominant signs into dysfunction of the spinal cord, cerebrum, cerebellum or multiple regions of the central nervous system. Detailed descriptions of pathologic lesions are beyond the scope of this article, however, the general location of these lesions is described to facilitate selection of appropriate samples for diagnostic testing. A brief review of the location of lesions and their relationship to clinical signs is provided. Some non-inherited conditions are briefly discussed to differentiate the many causes of CNS dysfunction in calves.

Résumé

La distinction entre les maladies héréditaires du système nerveux central (SNC) chez les veaux et les désordres acquis est importante à cause de ses ramifications importantes dans le programme de reproduction du troupeau et du pauvre pronostic qui leur est associé.

On connaît ou soupçonne plusieurs conditions héréditaires qui entraînent un mauvais fonctionnement du système nerveux central chez les veaux incluant l'encéphalomyélite progressive dégénérative, l'atrophie musculaire spinale, l'axonopathie dégénérative, la démyélinisation spinale, la citrullinémie, l'abiotrophie cérébelleuse, l'ataxie progressive, la parésie spastique, la maladie urinaire du sirop d'érable, l'œdème neuroaxial, les convulsions bovines familiales, les maladies de stockage, la lipodystrophie neuronale et la myélodysplasie.

Cette revue décrit brièvement le signalement et les signes cliniques communs associés à plusieurs conditions héréditaires connues ou soupçonnées causant un mauvais fonctionnement du SNC chez les veaux. Ces maladies sont catégorisées par la localisation des signes prédominants dans les dysfonctions de la moelle épinière, du cerveau, du cervelet ou de plusieurs régions du SNC. Une description détaillée des lésions pathologiques est au-delà des limites de cet article mais, toutefois, la localisation générale de ces lésions est décrite pour faciliter la sélection d'échantillons appropriés pour le test diagnostic. Une brève revue de la localisation des lésions et de leurs liens avec les signes cliniques est présentée. On discute de certaines conditions acquises pour différentier les multiples causes du mauvais fonctionnement du SNC chez les veaux.

Introduction

The differential list for dysfunction of the central nervous system (CNS) in calves is extensive and includes both inherited and non-inherited disorders. Clinically, it is often impossible to differentiate between these disorders. In most cases, clinical signs can be localized to dysfunction of one or more of the following areas of the CNS: spinal cord, cerebrum, cerebellum. Localiza-

tion of clinical signs and a comprehensive diagnostic work-up leads to a diagnosis of most non-inherited disorders, however, postmortem examination is usually required to confirm inherited disease. The following paper reviews a few of the many proven or presumably inherited CNS disorders of calves. Table 1 describes clinical signs of CNS dysfunction and relates them to specific locations in the CNS. The inherited disorders are categorized according to their clinically apparent location in the CNS, described in terms of reported breeds affected, location of distinguishing pathologic findings, salient clinical signs, mode of inheritance and other pertinent distinguishing characteristics. Non-inherited diseases of the CNS are briefly reviewed by categorizing them according to clinically apparent location in the CNS in order to provide the practitioner with a comprehensive set of differentials for CNS dysfunction in calves.

Spinal Cord Dysfunction

Progressive Degenerative Myeloencephalopathy (Weaver Syndrome)

Progressive degenerative myeloencephalopathy is reported in Brown Swiss calves.[4,28] Characteristic histopathologic lesions are located primarily in the ascending and descending tracts of spinal white matter. The disease is characterized by onset of ataxia at 5 to 8 months of age, followed by loss of proprioception and eventual recumbency.[28] Other clinical signs include weakness and varying degrees of dysmetria in the limbs. Hind limbs are more severely affected. Attempts to move rapidly may result in cessation of movement in the hind limbs, while the animal tries to pull itself forward with the forelimbs. Motor and sensory reflexes remain intact.[4] By 18 – 24 months of age, most animals develop severe ataxia of the pelvic limbs with markedly diminished proprioceptive reflexes and eventually become recumbent.[4] Clinically, this disease may resemble calves affected with vertebral body abscesses/fractures, spinal cord trauma or organophosphate toxicosis. The mode of inheritance is thought to be a simple recessive trait.[4,28] Diagnosis is largely made by signalment, clinical signs and histopathologic examination.

Spinal Muscular Atrophy

Spinal muscular atrophy has been reported in Brown Swiss,[41] Braunvieh,[10] Holstein-Friesian[34] and Red Danish[41] calves. Lesions are predominately located in the lower motor neurons of the cervical and lumbar intumescences of the spinal cord.[41] Review of 53 cases

Table 1. Clinical signs categorized by anatomic location in the central nervous system.

Location of lesion	Prominent clinical signs
Spinal cord	Ataxia
	- flexor/extensor weakness (limb dragging, buckling, trembling)
	- incoordination
	- swaying
	- limb crossing
	- abducted or adducted limb placement
	Dysmetria
	- hypermetria
	- hypometria
	Abnormal spinal reflexes
	- hyper-reflexia (upper motor neuron)
	- hyporeflexia (lower motor neuron)
Cerebrum	Seizures
	Coma
	Depression/change in mentation/abnormal vocalization
	Blindness
	Compulsive walking, circling
	Opisthotonus
	Head pressing/yawning
	Stiff neck (meningitis)
Cerebellum	Ataxia without weakness
	Intention tremors/head tremors
	Wide based stance
	Hypermetria
	Lack of menace reflex with no loss of vision
	Vertical or rotary nystagmus

reported the age of onset from birth to 8 weeks, with a mean of 3.1 weeks.[10,13,41] The mean duration of recumbency before death is 6.4 weeks. Clinical signs include weakness and hind limb ataxia progressing to recumbency. Profound muscular atrophy of the appendicular muscles, particularly of the hind limbs, is present. Axial muscles are also affected. Most calves develop bronchopneumonia in the terminal stages.[41] The disease is transmitted by a simple autosomal recessive gene.[13] Diagnosis is based on clinical signs and histopathologic findings. This disease should be considered when other causes of severe muscle atrophy, such as neurogenic atrophy or sarcocystis, have been ruled out.

Progressive Ataxia

Progressive ataxia is caused by a myelin disorder in pure and mixed breed Charolais calves.[32] Characteristic postmortem histopathologic lesions consist of eosinophilic plaques in the white matter of the cerebellar medulla and peduncles.[32,46] Clinical signs usually begin at about 6 months, but have been recorded to begin as late as 3 years of age. A swaying gait of the hind limbs, hyperreflexia, head nodding, tremors and full, pulsatile urination interspersed with urine dribbling of variable duration are consistent clinical signs.[32,46] Stiffness of the neck, aggressiveness and loss of proprioception have also been reported. By 2 years of age, most affected animals become recumbent. Muscle atrophy is not typically observed with this disorder. Antemortem diagnosis is suspected by clinical signs, breed affected and by ruling out other causes of hind limb ataxia (Table 2). While histopathologic lesions are present in the brain, clinical signs resemble those of a spinal cord lesion caudal to T2. Explanations for the disparity between lesions and clinical signs are beyond the scope of this paper, however, they may be found in the cited literature.[32,46] Although the disease is presumed to be inherited, the exact mode of transmission has not been elucidated.[32]

Spastic Paresis (Elso Heel)

Breeds of calves affected by spastic paresis include Holstein, Angus, Shorthorn, Charolais, Brown Swiss, Ayrshire, Simmental, Polled Hereford,[26] Maine Anjou, Gelbvieh[40] and Belgian Blue.[43] Reports of significant histologic lesions were not found, however, a decrease in muscle cell nuclear size in calves with spastic paresis has been observed.[42] The pathogenesis of the disease is not completely understood. Clinical signs usually appear between 2 and 6 months of age. The condition is characterized by asymmetric spasticity and hypertonia of one or both rear limbs. The gastrocnemius and superficial digital extensor muscles are spastically contracted. Extensor tone is normal when the calf is recumbent, but becomes excessive when the calf stands and attempts to walk. The result of the excessive extensor tone is an overextended hock while the animal is bearing weight. When standing, the affected limb is often held in extension with the toe held slightly off the ground (Figure 1). While walking, the overextended limb has to be advanced by circumduction (pendulum like) to avoid dragging the toes. The spasticity progresses until the animal eventually has difficulty rising.[26,40] The mode of inheritance is thought to be recessive with incomplete penetrance,[26] however, the definitive genetic basis remains unproven. Tibial neurectomy and superficial digital flexor tenotomy are surgical procedures described for treatment of spastic paresis, however, these animals should not be used for breeding.[42,43] Diagnosis is made by characteristic clinical signs. This condition should be suspected in any calf of appropriate breed with an abnormal hind limb gait when other etiologies are ruled out or less likely.

Neuraxial Edema

Two related nervous conditions of newborn Herefords have been described. Neuraxial edema affects predominately polled Herefords, while congenital brain edema is seen primarily in horned Hereford calves.[9,24] Differentiation of these syndromes can only be achieved by histopathologic postmortem examination of the brain, spinal cord and coxofemoral joints. Clinical differences observed between these calves are related to differences in distribution of lesions. Vacuolation of white matter in the brain and spinal cord characterize neuraxial edema, whereas animals with congenital brain edema not only have neuraxial vacuolation but hypomyelinogenesis as well.[9,12,20,24] Calves with either of these syndromes are affected at birth, are unable to rise and manifest extensor spasms upon stimulation. Calves with neuraxial edema tend to lie quietly and lack the ability to lift the head. When stimulated, calves develop marked extensor tonus and clonic spasms of the limbs and head.[12] Calves with congenital brain edema have shorter gestational lengths, and are unable to stand unassisted at birth, however, most can lift their heads. When assisted to stand, spontaneous and stimulus-responsive myoclonic extensor spasms with whole body rigidity are frequently observed. Reflexes are brisk and frequently accompanied by myoclonic jerks.[20] Macroscopic lesions of the coxofemoral joints are frequently observed in neuraxial edema, are traumatic in nature, and consist of hemorrhages and fibrosis in the joint capsule in addition to fractures of the articular cartilage and underlying bone of the acetabular fossa.[20] Both conditions are inherited in an autosomal recessive manner.[9,24] Due to presence of signs at birth, extensor spasms, myoclonus and occasional head spasms, this condition may be difficult to differentiate clinically from in-utero bovine viral diarrhea virus (BVDV) infection. Therefore, past history of BVD on the farm and post-mortem examination of the cerebellum for

Table 2. Inherited and non-inherited conditions categorized by clinically apparent area of dysfunction.

Apparent area of dysfunction	Inherited conditions	Non-inherited conditions
Spinal cord	-Weaver Syndrome -Spinal Muscle Atrophy -Progressive Ataxia -Spastic Paresis -Neuraxial Edema -Myelodysplasia	-Vertebral body abscess -Vertebral body fracture - Spinal cord trauma without fracture -Organophosphate toxicosis -Tetanus -Botulism -Copper deficiency -Vitamin E/Selenium deficiency -Sarcocystis -Tick infestation -Lupines -*Astragalus, Oxytropis spp.* intoxication -Upward patellar fixation
Cerebrum	-Citrullinemia -Maple Syrup Urine Disease -Congenital Hydrocephalus	-Bacterial meningitis -Bovine Herpesvirus 1 and 5 -Polioencephalomalacia -Neospora -Bluetongue and Akabane virus *in utero* exposure -Rabies, pseudorabies -*Haemophilus somnus* -Sodium ion toxicosis -Ammoniated hay toxicosis -Lead toxicosis -Hypoglycemia -*Astragalus, Oxytropis spp.* intoxication -Fungal infected Bermuda, Canary, Dallas grasses and ryegrass -Coccidiosis -Vitamin A deficiency
Cerebellum	-Cerebellar Abiotrophy -Storage Diseases -Cerebellar Hypoplasia	-*In utero* BVDV infection
Multiple locations	-Degenerative Axonopathy -Spinal Dysmyelination -Bovine Familial Convulsions	-Sarcocystis -Listeria -Otitis media/interna -Hypomagnesemia

hypoplasia would be valuable information to obtain while pursuing a definitive diagnosis.

Myelodysplasia

The term myelodysplasia encompasses such disorders as spinal dysraphism, syringomyelia and hydromyelia. Myelodysplasias are most commonly seen in Charolais calves and are often associated with cleft palate and arthrogryposis. Signs are caused by dilation of the central spinal canal and cavitation of portions of the spinal cord, therefore, the spinal cord is the appropriate post-mortem specimen.[29]

Calves are affected at birth with various degrees of arthrogryposis, inability to stand and most often remain in lateral recumbency. The muscle masses of affected limbs are reduced in size and tone. Varying degrees of sensory loss are also noted.[29] The mode of inheritance is unknown.[29] There are many toxic (*i.e.*, lupines) and infectious (*i.e.*, BVDV) causes of arthrogryposis and/or cleft palate in cattle. However, in Charolais calves these clinical signs should lead one to consider an accompanying spinal dysraphism of genetic origin.

Cerebral Dysfunction

Citrullinemia

Citrullinemia is reported in Holstein-Friesian calves. Characteristic histologic lesions are found in the

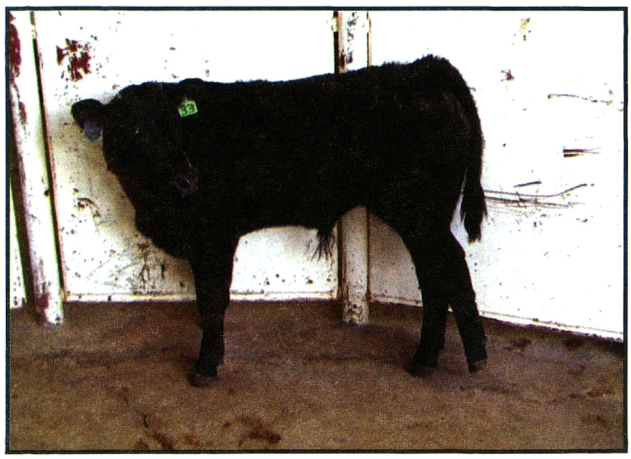

Figure 1. This calf has spastic paresis. Note the typical stance with the overextended hock and elevation of the toe.

cerebrum.[19] Clinical signs usually begin at 1 to 4 days of age and include apparent blindness, depression, head pressing, convulsions, terminal coma and death by 1 week of age. The disease is an autosomal recessively transmitted deficiency of arginosuccinate synthetase, which results in an increase in plasma citrulline. Clinical signs are believed to be due to hyperammonemia created by a dysfunctional urea cycle.[19] Dairy bulls can be screened for the defective genotype by DNA sequencing.[19,38] In addition to DNA sequencing, antemortem diagnosis is suggested by increased levels of serum citrulline. Clinically, meningitis, hypoglycemia and sodium ion toxicity as well as other non-inherited diseases (Table 2) would present with similar signs and should be ruled out before considering citrullinemia (Figure 2).

Maple Syrup Urine Disease

Maple syrup urine disease is a spongiform encephalopathy that is reported in polled Shorthorn and both polled and horned Hereford calves. Pathologic findings are located in the cerebrum.[21] Calves are normal at birth, however, clinical signs begin within the first week of life. Signs include marked depression, recumbency, opisthotonus, repetitive head tremors, stimulus-induced tetanic spasms, decreased spinal reflexes and convulsions. Calves usually die by day 10. Non-inherited disease rule-outs for these signs are similar to those described for citrullinemia. The name of the disease is derived from reports of "burnt maple syrup" smelling urine. The syndrome is due to a deficiency of branched-chain ketoacid decarboxylase which results in an accumulation of ketoacids. The mode of inheritance is thought to be due to an autosomal recessive trait. Although the lesions are characteristic of a spongiform encephalopathy, there is no mention in the literature of a prion involved in the pathogenesis or serving as the

Figure 2. This calf was diagnosed with bacterial meningitis, however, it would be difficult to differentiate these clinical signs from those of inherited causes of cerebral dysfunction.

etiology. The point mutation responsible for this syndrome can be detected in carrier animals by polymerase-chain reaction (PCR) based tests.[11,14,21,22] There is no known effective treatment.

Congenital Hydrocephalus

Congenital hydrocephalus is reported in Hereford and Shorthorn calves, however, many other breeds may be affected. Gross and microscopic lesions are located in the cerebrum. A domed skull, with or without ventricular dilation, is suggestive of this disease. Calves are born dead, or die within a few days of birth. These calves are usually recumbent and unable to rise and nurse. Other clinical findings include multiple ocular defects such as retinal detachment and dysplasia, cataracts, microphthalmia and persistent pupillary membranes.[8] This condition is inherited as a simple autosomal trait.[3,8,17] The ocular defects, in addition to the other neurological signs, might lead one to include BVDV in the differential list.

Cerebellar Dysfunction

Cerebellar Abiotrophy

Cerebellar abiotrophy is reported in Holstein calves. Histologic lesions are located in the cerebellum. Calves are normal at birth and at 3 to 8 months of age begin to display clinical signs characteristic of cerebellar dysfunction. Signs include truncal ataxia, base-wide stance, intention head tremors, hypermetria, hyperreflexia, opisthotonus and nystagmus (Figure 3). The first signs of disease occur suddenly and progress rapidly over several days.[27,45] The mode of inheritance is reportedly a recessive genetic defect.[27] Diagnosis is made by clinical signs, history and histologic examination of the cerebellum. Absence of clinical signs at birth differentiates this disease clinically from BVDV-induced cerebellar hypoplasia.

Storage Diseases

Inherited storage diseases include α-mannosidosis of Angus, Murray Grey, Simmental, Holstein and Gal-

Figure 3. This calf is displaying typical signs of cerebellar dysfunction. Note the wide-base stance. (Photo courtesy of Dr. Robert Kahrs)

loway calves[15] and β-mannosidosis of Saler calves.[5] Additionally, bovine generalized glycogenosis of Shorthorn and Brahman calves[31,37] and neuronal lipodystrophy of Angus and Beefmaster calves can be classified as inherited storage diseases.[35] Characteristic microscopic lesions of these conditions are located in the cerebellum.

The α-mannosidosis form is characterized by clinical signs beginning from 1 to 15 months of age with mild ataxia that develops after exercise. Other signs include aggressiveness and cerebellar signs such as mild intentional head tremors, hypermetria and base-wide stance. Most calves develop diarrhea. Ataxia and other neurological signs worsen, and after 3 to 4 months, most calves become recumbent, but some may survive longer before recumbency ensues. Neurological signs usually persist in these calves, and they fail to grow normally. The disease is caused by an autosomal recessive trait that decreases the activity of α-mannosidase, resulting in the accumulation of undigestible tetra-saccharides in lysosomes. The activity of α-mannosidase can be measured enzymatically to allow detection and elimination of heterozygote animals.[7,25]

The β-mannosidosis form is caused by a deficiency of β-mannosidase. Clinical signs include recumbency from birth, poor suckling reflex, a dome-shaped calvarium and small "squinty" eyes. The mode of inheritance is an autosomal recessive trait.[1] Assay for β-mannosidase activity in the plasma of herd members is useful in eliminating the disease.[5]

Bovine generalized glycogenosis (Pompes disease or Type II glycogenosis) is a storage disease in which two forms are described; the cardiac (infantile) form and the late onset form. The infantile form is characterized in Brahman and Shorthorn calves by unthriftiness, weakness, hyperesthesia, muscle tremor, ataxia, conscious proprioceptive deficits and recumbency beginning at 2 to 3 months of age. Calves often succumb to right-sided heart failure by 3 to 5 months of age. The late onset form of this disease is manifested in Brahman calves by a short course of illness followed by death at 8 to 9 months of age, while Shorthorns with this form may live longer than 1 year. The disease is caused by a single recessive allele with complete penetrance.[31,37] The activity of α-glucosidase can be measured in purified peripheral blood lymphocytes or tissues, allowing detection of carrier animals.[30]

Neuronal lipodystrophy has been characterized as a storage disease even though the specific biochemical lesion is unknown. Characteristic histopathologic lesions include neuronal vacuolation and intracytoplasmic, eosinophilic and sudanophilic inclusion bodies.[35] Clinical signs begin around 10 months of age and include depression, blindness, ataxia, circling, coma, and tonic-clonic convulsions. The mode of inheritance is unknown.

Cerebellar Hypoplasia

Cerebellar hypoplasia is a genetic defect of Hereford calves. Other breeds reported to have similar conditions, but with unconfirmed heritability, include Ayrshire, Shorthorn and Angus. Lesions are located in the cerebellum. Clinical signs are usually present at birth and include recumbency with extended limbs, ataxia and opisthotonus. The mode of inheritance is autosomal recessive.[8,16,23,39] The primary rule-out for this condition would be BVDV-induced cerebellar hypoplasia.

Multiple Location Dysfunction

Degenerative Axonopathy

A degenerative axonopathy of neonatal Holstein-Friesian calves has been described. Lesions can be found by extensive examination of the spinal cord, brainstem and midbrain.[18] Due to variations in the degree of severity of histologic lesions, the entire spinal cord should be submitted. Most calves are affected at birth and develop variable neurological signs including weakness and recumbency, hyperesthesia or depression, limb extension, head tremor, nystagmus, and apparent blindness. Opisthotonus in response to stimulus is also frequently reported. Other clinical signs include full body tremors to intermittent muscular spasms, reduced muscle tone and weaving head movements. This condition is thought to be inherited as reported cases are descendents of a common sire, however, the exact mode of inheritance has not been elucidated.[18]

Spinal Dysmyelination

Spinal dysmyelination of Braunvieh x Brown Swiss calves is one of many sporadically reported heritable demyelinating diseases.[2] Examples of other recognized syndromes of myelin disturbance include a bovine myelinopathy in Australian Murray Grey calves[33] and a primary demyelination disorder of Limousin calves.[36]

Appropriate post-mortem samples include the spinal cord, brainstem and midbrain.

Calves are affected at birth with lateral recumbency, opisthotonus and extension of the limbs. When placed sternally, calves eventually fall back into lateral recumbency. Reflexes are normal or increased. Pain perception is normal, as well as movement and strength of the tail.[2] Spinal dysmyelination is reportedly caused by an autosomally recessive trait.[2,33,36]

Bovine Familial Convulsions

Bovine familial convulsions and ataxia has been reported in Angus and Angus crossbred calves.[6,44] Histologic lesions are located in the cerebellar cortex.[44] The onset of clinical signs ranges from 2 to 3 hours after birth to 3 months of age. Calves initially develop tetaniform seizures that last from 3 to 12 hours. These episodes have been described in two forms. In the mild form, muscle tone increases leading to laborious and exaggerated movements. Calves develop generalized stiffness in the limbs in conjunction with a fine generalized tremor. In the severe form, clinical signs progress rapidly early in the course of the disease to recumbency, struggling, opisthotonus and paddling. The occurrence and length of seizures often decreases, rendering an animal with residual cerebellar ataxia. A defective autosomal dominant gene with incomplete penetrance presumably causes this condition.[6,44] There is no effective treatment.

Discussion

In addition to inherited diseases that cause central nervous system dysfunction, there are also many non-inherited conditions that present with similar clinical signs. Non-inherited conditions are broadly categorized as infectious, toxic, traumatic, nutritional and parasitic etiologies. Clinically, these non-inherited conditions can also be categorized by the predominant signs into dysfunction of one or more of the following areas of the CNS: spinal cord, cerebrum and cerebellum. Table 2 categorizes both inherited and non-inherited diseases of the CNS according to localization of predominate clinical signs.

Unlike the inherited diseases, many of the non-inherited conditions can be definitively diagnosed by antemortem testing. Therefore, a thoughtful and comprehensive clinical and laboratory workup of CNS dysfunction in a calf can significantly narrow the differential list. If an antemortem diagnosis is not obtained, the poor prognosis, limited specific treatment and potentially serious herd implications that accompany many of the aforementioned conditions will allow a practitioner to pursue a diagnosis by necropsy and submission of appropriate tissues for histopathologic examination.

If an inherited disorder is diagnosed, examination of the pedigree of that animal should be performed to avoid future matings that may lead to the birth of additional affected or carrier animals. If more than one calf is affected, examination of as many generations as possible would be beneficial to determine if these calves share a common sire or dam in their ancestry. Calves that survive such maladies should not be used for breeding.

Conclusions

There are many potential causes for clinical signs of central nervous system dysfunction in calves such that it is often not possible to differentiate between them. A major objective of the diagnostic process is to determine whether a case is potentially heritable or not. After a thorough diagnostic work-up, it should be possible to rule in or out many of the non-inherited diseases. Most of the inherited disorders require a complete postmortem examination to establish a diagnosis. In instances when specific tests are available to identify carrier animals that can potentially produce affected progeny, producers should be encouraged to incorporate them into the breeding program and cull affected animals.

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