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## Paroxysmal Disorders (6-Feb-2003)

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Several disorders are characterized by episodic, paroxysmal attacks during which affected animals may be acutely and dramatically incapacitated. Animals do not lose consciousness and are clinically normal between attacks. The pathophysiology of these disorders involves (or is considered to involve) abnormal neurotransmitter function, and microscopic changes are often not observed within the central nervous system. Episodic falling and muscle cramping, sometimes termed hyperkinesia (i.e., excessive motility or muscular activity) or muscular hypertonicity, are bizarre, paroxysmal neurological disorders that have been recognized in several breeds of dogs. Other paroxysmal neurological disorders include several sleep abnormalities of which narcolepsy is the best recognized.

An outline of this chapter is as follows:

### **Hyperkinetic Disorders**

- Episodic Falling
- Scotty Cramp

### **Sleep Disorders**

- Narcolepsy
  - Cataplexy
- Miscellaneous Sleep Disorders
  - Narcoleptic Hypersomnia
  - Periodic Leg Movements During Sleep
  - Rapid Eye Movement Sleep Disorder
  - Age-related Changes in Sleep-wake Rhythm in Dogs

### **Miscellaneous Paroxysmal Disorders**

- Familial Reflex Myoclonus
- Myokymia
- Syncope

### **Episodic Falling**

Episodic falling or hypertonicity is a well-recognized paroxysmal disorder in Cavalier King Charles Spaniels in the UK [1,2], and has been seen in the United States and Australia [67]. After a variable period of exercise, affected animals develop a peculiar bounding, pelvic limb gait in which the limbs may be abducted and appear stiff. Other signs may include a bunny-hopping gait, arching of the spine, vocalization and collapse. There is no loss of consciousness. Some affected dogs assume a "deer-stalking" posture, with increasing limb stiffness, falling, and legs held in extensor rigidity [2]. Episodes appear to be triggered by stress, apprehension, and excitement. Signs are typically first observed between 3 and 7 months of age. Animals are neurologically normal between attacks, which appear to be a life-long event. Affected dogs do not respond to anticholinesterases, but slight, temporary improvement may occur following diazepam treatment. A greater clinical improvement is reported following treatment with the benzodiazepine drug clonazepam which enhances GABA neurotransmission [67,70]. In one trial, clonazepam (at 0.5 mg/kg tid) resulted in almost complete remission of signs over a 2-year period [70]. Frequency of attacks is reportedly increased in some dogs using the antiepileptic drug carbamazepine (Tegretol) [1]. Results of hematology, blood chemistries, and electrodiagnostic testing are within normal limits. There is no evidence of lactic acidosis. No light microscopic lesions are seen in the central nervous system (CNS), peripheral nervous system (PNS), or viscera. Skeletal muscle appears normal microscopically, apart from presence of small vacuoles between myofibrils in some fibres stained with toluidine blue [2]. Histochemical staining using myosin ATPase, succinic dehydrogenase, and phosphorylase is normal. Ultrastructural alterations, however, have been reported in skeletal muscle,

which include dilatation and proliferation of sarcotubular elements, mitochondrial swelling and degeneration of cristae, and tubular proliferations in the region of the triads [3]. Wright stated that she was uncertain if the morphological changes were causally related to the clinical signs [2]. The pathogenesis of this paroxysmal condition remains enigmatic, although both genetic and neuropharmacological factors may be involved. In one study, 7 of 8 dogs were males and 5 had a common male ancestor that suggested an inherited trait [2]. It has been suggested [67,70] that this disorder has some similarities to hyperexplexia (startle disease) in people, a hereditary (autosomal dominant) pathological exaggeration of the normal startle response to auditory, somesthetic or visual stimuli which sometimes results in falling [68,69].

### **Scotty Cramp**

This is an inherited paroxysmal neurological disorder with a recessive mode of transmission in Scottish Terrier dogs [4-6]. Pharmacological studies suggest that the disorder is associated with a deficiency or relative deficiency of the inhibitory neurotransmitter serotonin (5-hydroxytryptamine), although serotonin brain content appeared normal in one study of affected dogs [7,8]. Anti-serotonin agents (e.g., p-chlorophenylalanine and amphetamine) markedly increase the severity of clinical signs, the intensity of which are reduced by a variety of drugs that increase cerebral serotonin concentration including tryptophan, phentolamine, nialamide and 5-hydroxytryptophan administration [5,9]. In one case report, ingestion of an excessive quantity of methionine induced Scotty cramp-like signs in a 2 year old Scottish Terrier that had not previously been seen to exhibit signs of the condition [10]. It was suggested that the methionine may have increased levels of the bi-methylated methionine compound, S-adenosylmethionine, which in turn might have acted as a methyl donor leading to an increased rate of serotonin methylation and consequently resulting in decreased levels of active CNS serotonin. Other studies suggest that the condition results from a complex interaction between serotonin and prostaglandins within the CNS [11] since anti-prostaglandin compounds (e.g., aspirin, phenylbutazolidin, penicillin G, flumixin meglumine, and indomethacin) increase the severity of clinical signs in affected dogs.

Clinical signs may be elicited by exercise, excitement, stress, and poor health. The condition may occur in animals at any age, however, signs tend to be more prevalent in young dogs less than 6 months of age. Affected dogs appear normal when at rest or at the beginning of exercise. As the exercise continues, clinical signs are usually observed that progressively increase in severity. Initial signs may be abduction of the thoracic limbs or arching of the lumbar spine, followed by pelvic limb stiffness, occasional catapulting of the pelvic limbs into the air, falling and curling into a ball, with the tail and pelvic limbs tightly flexed against the body. Respiration may momentarily cease and facial muscles may be contracted. Animals do not lose consciousness. Signs usually remit within 10 minutes. Multiple episodes may occur over a 24 hour period. The disorder is usually non-progressive.

Although there are no structural changes observed in the CNS, PNS, or in muscle of dogs with this episodic disorder, dural adhesions, meningeal hemorrhage, and bony irregularities causing dural and cortical impressions have been noted in one study involving affected Scottish Terriers [12]. These changes were seen in 10 of 12 young dogs (6 weeks to 18 months of age) and in 5 of 8 older dogs (3 to 11 years of age), suggesting possible inherited abnormalities that potentially affect the area of the motor cortex and account for the sporadic clinical signs under circumstances (e.g., stress, excitement, etc.) that increase arterial blood volume and brain volume/intracranial pressure [12]. To the author's knowledge, this theory has not been validated by other researchers.

Diagnosis may be based on historical information revealing a family history of cramping and on the clinical signs, since all laboratory tests are within normal limits. Signs can be induced using methylsergide, a serotonin antagonist, administered orally at a dosage of 0.3 mg/kg, and the animal exercised two hours later. Treatment consists of daily oral dosing of acepromazine maleate (0.1 to 0.75 mg/kg every 12 hours), or diazepam (0.5 mg/kg every 8 hours). Vitamin E (125 IU/kg/day) may also be effective [13]. Sometimes, behavioral modification or environmental change may be sufficient to avert clinical signs [13]. Note that clinical signs in older dogs may be induced or increased by concurrent disease.

A very similar condition has been reported in 2 young Dalmatian dogs, as well as in a Cocker Spaniel and a Wirehaired Terrier [14]. Muscle cramping or spasms involving the hindquarters, usually after but sometimes during exercise, and lasting for up to 5 minutes, is often seen in Norwich Terriers [15]. Muscle cramping characterized by weakness and exercise intolerance reportedly occurs sporadically in field-trial English Springer Spaniels with hereditary phosphofructokinase deficiency (see glycogenesis type VII).

### **Narcolepsy**

Human narcolepsy is a neurological disorder associated with abnormalities of rapid eye movement sleep and of sleep-wake control [16,17]. The clinical hallmarks are excessive sleepiness and cataplexy (an abnormal manifestations of rapid eye movement sleep [18]), although sleep paralysis and hypnagogic hallucinations may occur as well [19]. Narcolepsy occurs sporadically in dogs [20-26] and rarely, in cats [20,27]. In animals, although excessive daytime sleepiness may be seen (especially in the colony-housed narcoleptic dogs [28]), cataplexy is often the dominant clinical sign, which is characterized by sudden paroxysmal attacks of flaccid paralysis (muscle atonia) with conservation of consciousness, that may last from a

few seconds to more than 20 minutes, with sudden termination of signs [22,24,25]. Respiratory and ocular muscles tend to be spared, and swallowing and cough reflexes appear to be intact during cataplectic attacks. There is no fecal or urinary incontinence, no excessive salivation and no tonic rigidity of muscle. The attacks are frequently induced by excitement, such as eating, playing, sexual activity, or presence of owner or another dog. Attacks can be reversed by an external stimulus, such as petting or calling the animal's name. The frequency of attacks may vary from one every other day, to several hundred per day. Signs generally appear in affected animals prior to 6 months of age [29], although initial attacks can occur in mature animals. Results of a recent study using narcoleptic Doberman puppies showed that cataplexy onset (mean age around 10 weeks) corresponded to the emergence of adult-like REM sleep. The cataplectic attacks were more severe in the female puppies.

The pathogenesis of this disorder remains uncertain; however, an imbalance between cholinergic (e.g., hyperactive) and catecholaminergic (e.g., hypoactive) neurotransmitter systems within the CNS appears to be involved [30-34]. One mechanism might be through reduction in rate of locus coeruleus discharge (it is hypothesized that locus coeruleus activity contributes to the maintenance of muscle tone in waking; the rate is decreased by prazosin, an alpha 1 antagonist, and physostigmine, a cholinesterase inhibitor, both of which precipitate cataplexy) [35]. Some studies show that increased dopamine transmission mediates the wake-promoting effects of amphetamine-like stimulants [36], while others demonstrate preferential involvement of adrenergic systems in the control of cataplexy [37,38]. Recent studies also point to hypocretins (orexins) as important sleep-modulating neurotransmitters [18,39,40]. The hypocretins (orexins) are two novel neuropeptides (Hcrt-1 and Hcrt-2), derived from the same precursor gene, that are synthesized by hypothalamic neurons [72-74]. In addition, autoimmunity is considered by some researchers to play a role in the development of narcolepsy [41]. In human narcolepsy, most patients have non-familial (sporadic) narcolepsy, although one predisposing genetic factor is an HLA (human leukocyte antigen) gene of low penetrance [42]. Narcolepsy has been reported in many canine breeds including Doberman Pinscher, Miniature Poodle, Labrador Retriever, Dachshund, St. Bernard, Beagle, Afghan, Airedale, Welsh Corgi, Irish Setter, Malamute, Springer Spaniel, Standard Poodle, Wire-Haired Griffon, Australian Shepherd mix, Chihuahua-Terrier mix, Giant Schnauzer, and Rottweiler. Molecular studies have shown a degree of genetic heterogeneity in canine narcoleptics [43]. Autosomal recessive mutations have been reported in Doberman Pinschers and Labrador Retrievers involving a *canarc-1* gene with full penetrance [19], tightly linked with a marker homologous to the human micro-switch immunoglobulin gene (but not linked with the dog leukocyte antigen complex) [44], and a hypocretin (orexin) receptor 2 gene (*Hcrtr2*) [18,39] (the *canarc-1* mutation is a deletion of the hypocretin receptor 2 gene, although the mutation in these breeds is in a different region of the same gene). A milder mutation has also been identified in familial narcolepsy in Dachshunds [43]. No mutations in the *Hcrtr* gene were found in other, unrelated narcoleptic dogs [43]. Hypocretin mutations have been documented in human narcoleptics along with massive loss of hypocretin neurons and increase in glial fibrillary acidic protein in the hypothalamus [40,45,46]. Narcolepsy is also believed to be hereditary in Poodles [29].

There have been only a few recent reports of brain changes in canine narcoleptic patients. In a histochemical study using the amino-cupric silver stain on brain sections from canine narcoleptics, increased axonal degeneration was observed in the forebrain, including amygdala, basal forebrain (including the nucleus of the diagonal band, substantia innominata, and preoptic region), entopeduncular nucleus, and medial septal region [47]. Reactive neuronal changes were found in the ventral amygdala. Axonal degeneration was maximal at 2 - 4 months of age, while the number of reactive cells was highest at 1 month of age. These degenerative changes occurred before or at the time of onset of clinical signs. In another study, increased numbers of cholinergic neurons, identified by NADPH-diaphorase histochemistry, were found in the brains of narcoleptic dogs [48]. Microscopic brain lesions have occasionally been reported in cases of spontaneous narcolepsy in dogs. In light of the recent research on hypocretin neuropeptides and their effects on hypothalamic neurons, it is of interest that cataplectic-like attacks were observed in a 10 month old female Wirehaired Pointing Griffon with a hamartoma of the hypothalamus [49]. A coincidental relationship was considered in a 10 month old Argentine Dogo with narcolepsy and diffuse encephalitis in the forebrain and marked necrotic lesions in the ventral pontine area attributable to canine distemper encephalitis [50]. In a Giant Schnauzer with narcolepsy, malformation of the aqueduct of Sylvius and atrophy of the periventricular tissue in the midbrain were found at necropsy, but again, the authors were uncertain if these lesions were causally related to the narcolepsy [26]. Cataplectic episodes were also reported in a 12 week old Cairn Terrier puppy with multisystemic chromatolytic neuronal degeneration involving many nuclei in the brainstem, as well as in spinal cord, cerebellar nuclei, and sensory ganglia [51] (see Multisystem Neuronal Abiotrophy in Cairn Terriers).

Diagnosis is typically based on clinical signs. Attacks can be induced in most affected animals by exercise or eating. Signs can be alleviated for up to 45 minutes using an intravenous imipramine challenge test, at a dose of 0.5 mg/kg. Atropine sulfate (0.1 mg/kg, IV) is also reported to be a useful diagnostic test, providing immediate, temporary remission of signs for up to 3 hours [24]. The most common electrophysiological finding associated with narcolepsy/cataplexy in dogs is the rapid eye movement (REM) onset sleep and the shortened sleep cycle. During cataplectic attacks, there may be simultaneous

occurrence of REM sleep-like phasic events such as rapid eye movements, muscular twitching, variable vocalization, facial grimacing and chewing movements.

Prognosis is guarded. The disease is not in itself life-threatening and it may not get significantly worse with time. In humans, typical treatment for narcolepsy-cataplexy includes amphetamine-like stimulants for sleepiness and antidepressant therapy (e.g., non-sedating tricyclic antidepressants and serotonin/norepinephrine-reuptake inhibitors) for abnormal REM sleep (i.e., cataplexy, sleep paralysis, and hypnagogic hallucinations) [17,52]. For long-term treatment, animals may respond very favorably to tricyclic antidepressants, such as imipramine hydrochloride. Recommended dosage ranges from 0.5 to 1.5 mg/kg, PO tid or bid. Side effects of this drug in dogs include nervousness and sleepiness, which appear to be dose related. Methylphenidate hydrochloride (Ritalin), at 0.25 mg/kg, PO sid or bid, may also be effective. In a cataplectic Longhaired Dachshund (in which neither imipramine or methylphenidate were ineffective), treatment with dexamphetamine sulfate, at a total oral daily dosage of 5 mg, resulted in complete remission of clinical signs; however, treatment was stopped because of unacceptable behavioral side-effects (excessive sniffing of the ground, climbing into inaccessible places, hyperactivity, and refusal to eat) [25]. Although some dogs with severe signs early in life can show considerable amelioration of signs as adults, most dogs require lifetime treatment. In people, prolonged remissions are followed eventually by recurrence if drug treatment is stopped.

Several experimental drugs have been tested in colony narcoleptic dogs. These include CG-3703, a potent thyrotropin releasing hormone (TRH) analog, at 16 to 28 mg/kg PO, which significantly reduced cataplexy and daytime sleep, without changes in general behavior, heart rate, blood pressure, rectal temperature, blood chemistry or thyroid function [53]. In additional studies, systemically administered hypocretin-1 (*Hcr1-I*) had a dramatic effect on canine narcoleptics (increased activity level, longer waking periods, a decrease in REM sleep without change in nonREM sleep, reduced sleep fragmentation and a dose-dependent reduction in cataplexy were noted) [54]. In other canine studies, both acute and chronic oral administration of sulpiride (300 mg/dog, 600 mg/dog), a dopamine D2/D3 receptor antagonist, also significantly reduced cataplexy without noticeable side effects [55].

### **Miscellaneous Sleep-related Disorders**

Narcoleptic Hypersomnia - This condition, characterized by inappropriate and excessive daytime sleepiness, lethargy, and difficulty in arousing from sleep, was observed in a 6 month old Labrador Retriever dog [56]. Rapid eye movement and paddling within a few minutes of sleep onset were occasionally observed. Physical and neurological examinations, blood (including arterial blood gas) and urine analysis, and EKG were normal. Food-elicited cataplexy testing was negative. Electroencephalography revealed excessive slow wave (6 - 10 Hz, 20 - 45  $\mu$ v) activity. The dog was successfully treated using the tricyclic antidepressant protriptyline (Vivactil), at 10 mg PO per day. Continued treatment was necessary.

Periodic Leg Movements During Sleep - Results of a recent study indicated that narcoleptic dogs exhibited jerky, unilateral or bilateral slow leg movements during sleep characterized by repetitive dorsiflexions of the ankle, lasting 0.5 - 1.5 s, and occurring at regular intervals of 3 - 20 s [57]. These movements were considered to be similar to an idiopathic sleep disorder in humans, termed periodic leg movements during sleep (PLMS). Pharmacological studies suggested that altered dopaminergic regulation in canine narcolepsy may play a critical role in both cataplexy and PLMS. Presumably, the above-mentioned treatment aimed at controlling cataplexy should also control PLMS in narcoleptic dogs.

Rapid Eye Movement Sleep Disorder - Another, sporadic sleep disorder has been reported in a 15 month old cat in which violent seizure-like movements (pelvic limb movements sufficiently vigorous to propel the cat from a couch to the floor) occurred only during REM sleep (demonstrated by simultaneous electroencephalographic and electromyographic recordings) [58]. The episodes were not responsive to phenobarbital and a cause was not determined. The cat was easily aroused from these paroxysmal episodes and appeared immediately alert and without evidence of confusion. The cat, which was otherwise healthy, continued to have normal motor behavior during wakefulness and the abnormal sleep activity for 2.5 years after first presentation.

Age-related Changes in Sleep-wake Rhythm in Dogs - Results of recent studies indicate abnormalities in wakefulness (fragmentation of wakefulness in the daytime and a sleep disruption in the night), slow wave sleep (increased during daytime), and paradoxical sleep (reduced) in older dogs [75]. These changes may be associated with altered autonomic balance in the aged dogs.

### **Miscellaneous Paroxysmal Disorders**

Familial Reflex Myoclonus - This disorder has been reported in Labrador Retrievers puppies [59,60]. The pathogenesis is unknown. Clinical signs develop in puppies at about 3 weeks of age and are characterized by paroxysmal muscle spasms and progressive muscle stiffness to the point where affected animals are unable to walk or rise without assistance. Animals

lay in lateral recumbency and develop generalized extensor rigidity and opisthotonus in response to handling, voluntary activity and auditory stimuli. During severe episodes, respiratory distress and apnea can be observed, along with facial and masticatory muscle contracture and arching of the spine associated with paraspinal contractions. The extensor rigidity mimics generalized strychnine poisoning. Animals tend to relax in a quiet environment (in fact, at rest, affected animals appear normal). There is no evidence of muscle pain or percussion dimpling. Neurological deficits are not detected. Electromyographic recordings after various stimuli are characterized by intermittent bursts of giant polyphasic action potentials (0.5 - 15 mV). There are no myotonic discharges and motor nerve conduction velocities are normal. Results of urinalysis, hematology, blood chemistries, and muscle and nerve biopsies are within normal limits. No lesions are seen in the brain or spinal cord. Prognosis is guarded to poor. Therapeutic trials with diazepam (at 0.5 to 2.0 mg/kg PO, tid) alone or with phenobarbital (at 2.2 to 5.0 mg/kg PO bid) provides partial relief from the tonic spasms, although episodes can still be induced. Intravenous pentobarbital abolishes all signs of rigidity. The disorder may be genetic since in one study, the grandsire of the affected litter had sired 2 previous litters containing similarly affected pups. In the two reports to date, affected to normal puppy ratios have been 2:5 and 3:5 [59,60]. A defect in glycine, the major inhibitory neurotransmitter in the spinal cord, or altered genetic regulation of the spinal cord glycine receptor, has been suggested as the basis for this disorder [60].

**Myokymia** - A novel disorder clinically characterized by intermittent, rhythmic, vermicular movement of muscle groups in all four limbs leading to collapse into lateral recumbency (but without loss of consciousness) has been reported in a Yorkshire Terrier [76]. Signs began around 11 months of age. No neurological abnormalities were detected. Hematology and blood chemistries were normal apart from a mild increase in serum creatine phosphokinase levels. No lesions were seen in a muscle biopsy. Dramatic improvement in signs occurred with procainamide therapy (62.5 mg PO, tid). Signs returned on cessation of therapy.

Dramatic, paroxysmal attacks may be seen in animals with seizures (see epilepsy) and syncope. Seizures are the clinical manifestation of functional disturbances of the brain caused by hyperexcitable cortical neurons and animals may or may not lose consciousness [61]. **Syncope** refers to rapid loss of consciousness and postural tone caused by reduced cerebral blood flow [62]. It is most commonly associated with cardiovascular problems (e.g., dysrhythmias) but also may be related to autonomic perturbations, such as vasovagal syncope and carotid sinus sensitivity [63,64,77]. Defecation syncope and pulmonary thromboembolism has been reported in a cat [78]. Primary neurological disorders are extremely unlikely to cause syncope [62]. Painful, episodic muscle cramps affecting thoracic and pelvic limbs have been reported in two standard Poodles diagnosed with hypoadrenocorticism (the dogs were being treated with fludrocortisone acetate and prednisone) [71]. Neurological examination was normal between episodes. Serum biochemical abnormalities included hyperalbuminemia, azotemia, hyponatremia, hypochloremia, and hyperkalemia. Changing treatment to desoxycorticosterone pivalate resolved the electrolyte abnormalities and the episodes of muscle cramping in both dogs. Episodic weakness, collapse, and paralysis may occur with hyperkalemic myopathy. Episodic weakness, exercise intolerance, and acute onset of a stiff-stilted gait may be seen in animals with hypokalemic myopathy. Paroxysmal general body tremor and collapse into sternal recumbency associated with exercise or excitement has been reported in a young Great Dane with central core myopathy. Note that some forms of hyperkinesia [65] and episodic states, such as tail chasing [66], represent behavioral disorders. Hyperkinesia also occurs often in cats with hyperthyroidism. Periodic infarctions as a result of intravascular lymphomas may result in episodic neurological signs in dogs (see Infarction). Intermittent forelimb lameness has been reported in dogs with hypothyroidism (see Hypothyroid Neuropathy).

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