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NARCOLEPSY:
MORE COMMON THAN YOU THINK?

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INTRODUCTION

The sleep disorder narcolepsy has been recognized in several species, including humans, dogs, horses, and cattle. In human patients, narcolepsy is characterized by a tetrad of signs. The predominant sign is excessive daytime sleepiness with irresistible sleep attacks, and some human patients experience rapid-eye-movement (REM) onset sleep. Excessive sleepiness may be accompanied by one or more of three auxiliary symptoms: cataplexy, sleep paralysis, or hallucinations. The most common of these is cataplexy, which is a sudden loss of muscle control during which consciousness is maintained.

Narcolepsy in horses was first identified in "fainting" Suffolk foals in 1924, and has since been characterized as a rare sleep disorder manifested by cataplexy and excessive sleepiness. Although the true incidence of equine narcolepsy remains unknown, it appears that the disorder is more common than previously recognized. There appear to be two syndromes of equine narcolepsy, the first in which animals are affected at or within a few days of birth and the second in which animals are first affected as adults. In some neonatal foals, there may be persistence of fetal sleep patterns and the condition may improve with time.

PATHOPHYSIOLOGY

Hereditary factors are clearly involved in the development of narcolepsy in both people and dogs. A familial occurrence of narcolepsy was reported in Miniature Horses, with the onset of signs being at or within a few days of birth. The role of genetics in narcolepsy in adult horses remains unclear, and the condition has been recognized in a variety of breeds. In a few cases, affected relatives have been identified.

In all species, including horses, there are generally no gross or histologic lesions in the central nervous system in cases of narcolepsy, suggesting a biochemical basis for the disease. The regulation of sleep involves complex interactions between neuronal networks. Initially, work was focused on the role of acetylcholine and biogenic amines, including dopamine, serotonin, epinephrine and norepinephrine. Recently, hypocretins (orexins) have been implicated in the etiology of narcolepsy in dogs, laboratory animals and human patients. The hypocretins are two hypothalamic neuropeptides which appear to have roles in regulating sleep, appetite, neuroendocrine function and energy metabolism. In canine families with autosomal recessive narcolepsy transmission (Doberman pinschers, Labrador retrievers), a mutation in the hypocretin receptor-2 gene was identified. The mutation alters the normal developmental course of hypocretin levels. In humans, most cases of narcolepsy are not linked to hypocretin ligand or receptor mutations, but are associated with undetectable levels of hypocretin-1 in the CSF and a loss of hypocretin producing neurons. The HLA association in humans suggests possible autoimmune activity against hypothalamic hypocretin-containing cells. The role of hypocretins in equine narcolepsy is unknown, but is under investigation.

ADULT ONSET NARCOLEPSY

Signalment: In a five year period, 23 adult horses were diagnosed with signs consistent with narcolepsy at Washington State University. There appears to be no breed or sex predilection in adult onset narcolepsy. The age at which signs are first observed by the owner is highly variable, ranging from 2 to over 20 years.

Clinical signs: The only abnormality on basic physical examination is the presence of abrasions in most, but not all, affected horses. In particular, hair loss and thickening of the skin over the dorsal aspect of the fetlocks is common. Affected horses typically do not demonstrate any neurologic deficits between narcoleptic episodes. The clinical manifestations of narcolepsy vary both between individuals and between episodes; however, cataplexy, ranging in severity from mild weakness to total collapse, is recognized in most cases. The most common behavior observed is a gradual lowering of the head followed by buckling of the forelimbs. The majority of animals begin to fall forward, resulting in trauma to the dorsal aspect of the fetlocks and occasionally to the carpi. Buckling of the hindlimbs is sometimes observed. During most attacks, horses regain strength and stand without falling. When forced to ambulate during an episode, some horses appear ataxic, stumbling as if sedated, before arousal. Occasionally horses do fall completely during an episode. These horses generally regain awareness and rise shortly after falling; only rarely is REM sleep observed after collapse.

Affected horses also exhibit frequent periods of sleepiness, standing base-wide with their eyelids partially closed and their heads lowered. This behavior often occurs at an inappropriate time, such as during saddling. Episodes of sleepiness have been observed both immediately prior to an episode of cataplexy and independently. Horses typically can be aroused by noises or touch during episodes of sleepiness or cataplexy and subsequently appear alert.

Narcoleptic episodes in dogs can often be stimulated by food or play, and narcolepsy associated with feeding has been reported in the horse. Some other reported precipitating events include tying in the wash rack or saddling. However, signs are most often observed in horses while they are in a stall or at pasture without a particular inciting event. Importantly, sleepiness and cataplexy have been reported during riding.

An accurate assessment of the number of narcoleptic attacks is limited, as most horses are not under continual observation. However, it appears that the frequency of narcoleptic attacks is highly variable. Although in some cases there may be a temporary improvement in signs after a change in environment, it appears that permanent recovery is uncommon.

Diagnosis: Establishing a definitive diagnosis of narcolepsy in the horse is difficult and diagnosis is currently based primarily on the history, characteristic clinical signs, and exclusion of other possible causes of excessive sleepiness or collapse. One problem in making a diagnosis is that episodes may be difficult to observe, especially since a change in environment may cause remission of signs; therefore, it is often helpful to have the owners' videotape episodes. Distinguishing cataplexy from other causes of episodic weakness is important, since cataplexy is virtually unique to narcolepsy. Syncope and seizures are important differentials for narcolepsy. In general, syncope is characterized by acute collapse without warning and, unlike narcolepsy, is not preceded by a gradual lowering of the head and drowsiness. Increased focal or generalized tonic-clonic muscle activity and post-ictal depression are typically seen with seizures, but are absent in narcolepsy. In addition, excessive sleepiness can be seen in horses that have an underlying condition that prevents them from lying down to sleep, such as musculoskeletal or thoracic disease. Therefore, a complete history and thorough physical exam are essential.

Laboratory tests, including routine analysis of CSF, are generally normal and help to rule out other disease processes. EEGs may be normal or may reveal fast waves of REM activity during episodes. Pharmacologic testing has been advocated to support the diagnosis of narcolepsy in animals, and has been reported in horses. Most often, physostigmine salicylate, a cholinergic agonist that penetrates the blood-brain barrier, has been administered to elicit episodes of sleepiness and cataplexy. However, response to the drug between individuals is highly variable, and Sweeney reported a variable response to repeated administration in the same horse. In one series of narcoleptic horses challenged, only 1/10 horses had a positive response.

It has been reported that equine protozoal myeloencephalopathy can cause signs of narcolepsy. This has not been seen in narcoleptic horses examined at Washington State University. However, it is recommended that testing for EPM be considered.

Treatment: A number of drugs have been used in the management of narcolepsy in human patients. One of the more commonly used drugs is imipramine, a tricyclic antidepressant which inhibits cataplexy primarily by blockade of norepinephrine and serotonin reuptake. Imipramine (0.5 – 1.0 mg/kg q 12 h, orally) has been used in horses with some success, but there are no controlled therapeutic trials investigating its use.

It has been speculated that oral tyrosine, which may increase dopamine concentrations, could improve clinical signs of narcolepsy. In one study, 8 human patients with narcolepsy were treated with oral tyrosine (average dose 100 mg/kg/day). Clinical signs improved by 6 months in all patients, but there were no control patients in the study. Anecdotally, tyrosine has been of benefit in some, but not all, narcoleptic horses.

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