REPRODUCTION REPORT

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BLOOD TEST AVAILABLE FOR HYPERKALEMIC PERIODIC PARALYSIS IN QUARTER HORSES

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Hyperkalemic periodic paralysis (HYPP) is a muscle disease which has been reported in certain lines of registered Quarter Horses, Appaloosas and Paints. Affected horses often display well developed muscles and are often very successful when shown in halter classes. The condition may be seen in stallions, mares or geldings, can cross breeds and, therefore, is not limited to stock-type horses. The disease also closely resembles a heritable disease in humans. Studies at the University of California at Davis Equine Research Laboratory have produced much needed information about the genetics, cause and control of HYPP in horses. An accurate blood test has been designed for diagnostic purposes as well as to identify carriers of the disease.

Signs of the disease

Hyperkalemic periodic paralysis is characterized by sporadic attacks of muscle tremors (shaking or trembling), weakness and/or collapse. Attacks can also be accompanied by loud breathing noises resulting from paralysis of the muscles of the upper airway. Occasionally, sudden death can occur following a severe paralytic attack, presumably from heart failure or respiratory muscle paralysis.

Attacks of HYPP can take various forms and commonly have been confused with other conditions. Because of the muscle tremors and weakness, HYPP often resembles exertional rhabdomyolysis ("tying-up" syndrome). "Tying-up" syndrome can be caused by any different circumstances, including exercising a horse beyond the capacity to which it has been trained, as well as nutritional deficiencies and metabolic diseases. A distinguishing feature of this disease from "tying-up" syndrome though, is that horses usually appear normal following an attack of HYPP. Horses with "tying-up" syndrome, on the other hand, tend to have a stiff gait and painful, firm muscles of the hind limbs, rump and/or back. "Tying-up" syndrome is also generally associated with some type of exercise. HYPP, by contrast, is not usually associated with exercise, but occurs when horses are at rest, at feeding time, or following a stressful event such as transport, feed changes, or concurrent illness.

Because a horse may be down and reluctant or unable to stand during an HYPP attack, many owners have thought their horses were experiencing colic. HYPP has also been confused with seizures due to the pronounced muscle trembling and collapse. Unlike seizures and other conditions that cause fainting, however, horses with HYPP are conscious and aware of their surroundings during an attack and do not appear to be in pain. Respiratory conditions and choke have also been confused with HYPP because some horses make loud breathing noises during an attack.

Causes of attacks

Potassium is an important electrolyte and is vital for the normal function of muscles and nerves. In fact, every cell in the body contains potassium, as it is vital for maintaining the cell's volume and electrical activity. High concentrations of potassium are present in the normal diet of horses and large amounts are found in forages such as pasture grasses and hays.

Regulation of body potassium is very complicated and is strictly controlled by hormones throughout the body produced by the kidneys, adrenal gland, thyroid and pancreas. Because normal horses commonly consume an excess of potassium in their diets, the kidneys must excrete excess potassium in urine. Initially, it could not be determined whether this disease was caused by a disorder in potassium regulation or by a disorder of muscle function. Studies of kidney, adrenal gland and thyroid function in horses with HYPP were normal. Investigations of muscle function in these horses, however, revealed a different story.

In early studies, abnormalities in the skeletal muscle by electromyography (EMG) were observed. Electromyography measures the electrical activity present in selected muscles. In affected horses, the muscles displayed a wide variety of abnormalities, specifically spontaneous activity from muscles under normal stimulation. These recordings demonstrated that the affected horses' muscles were hyperexcitable (overly excitable). Even when the horses appeared normal, in between attacks, the abnormalities were reproducible. These abnormalities were also observed when the horses were under general anesthesia and under the influence of nerve blocking agents. This proved the theory that the muscle was abnormal.

Abnormal electrical activity within muscle fibers occurs in other muscle diseases as well as HYPP, so the abnormal EMG findings are are not enough to definitively diagnose HYPP. Nonetheless, repeated episodes of muscle weakness or tremors in offspring of an affected sire or dam coupled with abnormal EMG findings would be highly suggestive of

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HYPP.

Collaborative studies with human physiologists Drs. Joel Pickar and Richard Carlsen of the University of California Davis School of Medicine and Dr. Jack Snyder of the Veterinary Department of Surgery led to the development of a specialized muscle biopsy procedure for horses which allowed researchers to isolate and study small muscle strips in a laboratory setting rather than performing research on the whole horse. Results from these studies confirmed that the isolated muscle was hyperexcitable and that there were abnormalities in sodium and potassium levels.

In horses with HYPP, studies revealed a defect affecting a protein called the voltage-gaited sodium channel, a tiny gateway in the membrane of muscle cells. This gateway controls the movement of sodium particles in and out of the muscle cell. These sodium particles carry a charge that changes the voltage current of a muscle cell, allowing it to contract or relax. In horses with HYPP, the regulation of particles through the sodium channel occasionally fails, disrupting the normal flow of ions in and out of the muscle cell, causing uncontrollable muscle twitching or complete muscle failure.

Further studies using molecular genetics revealed a mutation at one important site in the gene responsible for sodium and potassium regulation. This mutation allows the production of an abnormal protein which alters the structure and function of the sodium channel. As a result of these uncontrolable muscle contractions, potassium leaks from inside the muscle cell into the bloodstream, thus, raising the blood potassium concentration. The identification of this gene mutation is the basis for the blood test used to diagnose HYPP.

An inherited trait in horses: breeding trial results

In humans, HYPP is inherited as a dominant trait which is not sex-linked or carried on the X or Z chromosomes, and either sex may carry the trait. The proportion of individuals carrying a genetic defect which actually demonstrate signs of the disease is called penetrance. Sometimes, an individual can carry a genetic defect, but may never show signs of disease. In humans, HYPP has a high penetrance, meaning that the majority of individuals carrying the gene will demonstrate signs of disease at some time during their lives.

The mode of inheritance of the disease in horses has been suggested to be similar, although there had been no definitive studies to prove this theory. The purpose of the breeding study was to document, in a laboratory setting, the mode of inheritance of HYPP in horses through a controlled breeding study.

Four Quarter Horses (one stallion and three mares) with HYPP were bred to unaffected horses to determine the genetic basis of the disease. The first trial consisted of breeding the affected stallion to an affected mare. Three offspring (two colts and one filly) were obtained using embryo transfer techniques and all three foals were affected with HYPP. This initial study proved that the condition was heritable, but could not distinguish if the trait was dominant or recessive.

The second trial consisted of breeding the affected stallion to 11 unaffected mares of different breeds. The three affected mares were bred to an unaffected Quarter Horse stallion. Seventeen foals were produced from these breedings. All foals were tested for HYPP at two months of age. Of the17 offspring, 10 were affected with HYPP, proving that HYPP is a dominant trait.

Because HYPP is a dominate trait, the breeding of an affected mare or stallion to a normal horse will result in approximately 50% of the offspring carrying the trait. If two affected horses are bred, then at least 75% of the foals will be affected. The breeding of a normal offspring from an affected horse to another normal horse will result in normal offspring.

Prevention and control of HYPP attacks

During a severe attack of HYPP, emergency treatment from a veterinarian is necessary. For long term therapy, many horses can be managed by exercise and diet control alone. Regular exercise and access to a large paddock or pasture is preferred over stall confinement. Maintain a regular feeding schedule, preferably equally spaced, two to three times per day. Avoid rapid changes in feed, such as bringing a horse off pasture grass and immediately switching to alfalfa hay. Most horses improve when the potassium content in the diet is decreased.

An analysis of feed can be very helpful in problem situations. Oat hay contains approximately 1.4% potassium, alfalfa hay - approximately 2.5%, timothy hay - approximately 2.0 - 2.5% potassium and molasses - approximately 6% potassium. The HYPP horses at the Equine Research Laboratory do well on a diet of half alfalfa and half oat hay. Feeding grain such as oats, corn and or barley (each contain only 0.5% potassium) two to three times daily and access to a salt block can be helpful. If dietary management is not sufficient to prevent attacks, then treatment with a diuretic (acetazolamide) can be very helpful. Consult your local veterinarian for proper diagnosis and further recommendations on treatment.

Eliminating this disease from the horse industry

The major focus of this study has been to develop the use of a genetic marker associated with HYPP to identify affected horses to assist veterinarians and breeders in controlling the disease. In collaboration with Dr. Eric Hoffman, a molecular geneticist from the University of Pittsburgh School of Medicine, a more-specific HYPP gene probe was created using DNA from the affected Quarter Horse stallion. This gene probe offers breeders and veterinarians a tool which can be applied as a safer and more reliable diagnostic test for this disease.

Affected horses which are carriers of this genetically determined disease have many desirable traits. This is the reason that many of these horses are so successful in the show ring. In a recent report by Dr. Jonathan Naylor of the University of Saskatchewan, over 50,000 registered Quarter Horses are related to known carriers of the disease. However, the disease is not widespread in the Quarter Horse breed and only involves certain lines of halter type horses. At the present time, the disease has not been recognized in racehorses or endurance horses.

The recently developed genetic market test for this disease will allow breeders to identify carriers of HYPP and thus, direct their breeding programs. To eliminate this trait from certain lines, stallion and mare owners should have their horses tested prior to breeding and select normal horses for their breeding stock.

Myths about HYPP

Some people have felt that the disease can be diluted out and not carried to distant generations. This is false because an affected horse has just as much chance to pass on the trait as the affected parent which passed the gene to him. Some people also believe the horse will "grow out of it." This is not true. For unknown reasons, attacks of HYPP tend to occur most often at the beginning of intense training and fitting for shows (age three to seven years old). It is important to realize that horses with HYPP are affected for life. It is possible that older horses do not experience the same conditioning stresses as young horses or that owners have discovered the best management strategies for the older horses with HYPP.

Some people also think that if a horse does not show any signs up to a certain age, it does not carry the trait. Unfortunately, this is not the case. Once again, horses with HYPP are affected for life. There was a stallion and a broodmare with HYPP who did not show signs of the disease until ages 8 and 15, and both horses only experienced one isolated attack.

Owners and breeders of affected horses should inform prospective buyers of the management constraints these horses have and the potential for future episodes of HYPP. (*The Horse Report.*)

Testing

To have a horse tested for the specific DNA mutation causing HYPP, please send a whole blood sample in an EDTA vacutainer tube (a purple-topped tube) labeled with the horse's name, name of the owner or responsible agent, and a copy of the horse's pedigree. Please include a check for $50 per sample made payable to "UC Regents." For more information, call (916) 752-7416. Send sample to: Dr. Sharon Spier, Dept. of Medicine, Rm 2121 MS1-A, School of Veterinary Medicine, University of California, Davis, CA 95616