REVIEW ARTICLE

ARTICLE DE REVUE

Equine hyperkalemic periodic paralysis: Review and implications

Jonathan M. Naylor

Abstract

The purpose of this review is to present an up-to-date summary of the signs, diagnosis, treatment, and implications of equine hyperkalemic periodic paralysis. The review encompasses all original articles published between 1986 and early 1993. Hyperkalemic periodic paralysis is the result of a genetic mutation in the skeletal muscle sodium channel gene. It is inherited as an autosomal dominant trait; most affected horses are heterozygotes. The classical signs are muscle fasciculation, spasm, and weakness associated with hyperkalemia. However, these signs are only rarely observed in affected horses. Potential sequelae to attacks are abrasions and involuntary recumbency; these problems are not specific for hyperkalemic periodic paralysis, but they occur more frequently in hyperkalemic periodic paralysis-affected horses. It is also likely that hyperkalemic periodic paralysis results in greater muscle mass. There are suggestions that homozygotes may be more severely affected and show signs of upper respiratory obstruction as foals. The practitioner needs to be aware of the tests for hyperkalemic periodic paralysis, and their limitations, so that he can properly diagnose this condition. The industry has the difficult problem of deciding whether or not testing should be mandatory and the fate of positive horses.

Résumé

L'hyperkaliémie paralytique périodique chez les équins : revue et conséquences

Cette étude présente une mise à jour des signes cliniques, du diagnostic, du traitement et des conséquences de l'hyperkaliémie paralytique périodique chez les équins.

Cette revue englobe toute la littérature publiée de 1986 jusqu'au début de 1993. Cette pathologie provient d'une mutation génétique du gène transmettant la voie du sodium au site des muscles squelettiques. Elle est transmise par caractère autosomal dominant et les chevaux hétérozygotes sont les plus atteints. Les signes cliniques typiques sont une fasciculation musculaire, des spasmes et une faiblesse associés à l'hyperkaliémie. Toutefois, ces signes ne sont que rarement observés chez les sujets atteints. Les séquelles des crises peuvent inclure des abrasions et un décubitus involontaire. Bien que ces problèmes soient non spécifiques à la pathologie, ils se produisent plus fréquemment chez les chevaux atteints d'hyperkaliémie paralytique périodique. Il est aussi probable que cette anomalie résulte en une masse musculaire plus grande. On a aussi fait allusion que les homozygotes seraient plus sévèrement atteints et qu'ils présenteraient des signes d'obstruction des voies respiratoires supérieures étant poulains.

Les praticiens doivent être informés des épreuves de diagnostic de l'hyperkaliémie paralytique périodique et de leurs limites afin de diagnostiquer adéquatement cette condition. L'industrie a le choix difficile de décider si le dépistage devrait être obligatoire et de décider du sort des chevaux dont le résultat est positif. *(Traduit par Dr Thérèse Lanthier)*

Can Vet J 1994; Vol 35: 279–285

Introduction

Hyperkalemic periodic paralysis (HPP) is a relatively new genetic disease of quarter horses characterized by muscle spasm and weakness. Its importance lies in the fact that many horses carry this defect and in the severity of clinical signs, particularly in homozygotes. In this article, the literature regarding equine HPP is reviewed, and the implications of the disease for veterinarians and horse owners are discussed. Recently, HPP has received much attention in the lay press and many horse owners are interested in the condition. There have been many advances in our knowledge of this disease, and the purpose of this review is to make it easier for the practitioner to be informed about this condition.

Literature reviewed

Articles on equine HPP were found by searching three data bases. My personal data base was searched for articles containing the terms HPP and equine. In June 1993, the CD-ROM version of Index Medicus (SilverPlatter Information Inc., Norwood, Massachusetts) was searched for the terms hyperkal* (to cover both British and North American spellings of —(a)emic) and periodic. This search used disks for the period

Department of Veterinary Internal Medicine, Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, Saskatchewan S7N 0W0.

TABLE 1. Sources of information for this review

Source	Number of original peer-reviewed articles	Total number of articles
Personal database	12	34
Index Medicus	8	8
Commonwealth Agricultural Bureau	9	17

1986 to May 1993, inclusive. Articles based on equine research were then selected manually. The CD–ROM version of the Commonwealth Agricultural Bureaux database (SilverPlatter Information Inc.) was searched for the term hyperkal*, and articles pertaining to HPP in horses were selected manually. The search period was from 1984 to 1992, inclusive. The year 1986 was selected for the beginning of these searches, because this is the year in which the first publications of equine HPP appeared (1,2).

Articles in the Proceedings of the American Association of Equine Practitioners were included as original, if the methods were clearly stated and the information did not subsequently appear as an original article in a peer reviewed veterinary journal. The total number of articles and the number of refereed articles presenting original data found by the various search methods are shown in Table 1. This review encompasses all the original articles on HPP in horses found in the above searches. Other sources of information are included, if they provide additional information on HPP. In addition, selected references on the pathogenesis of HPP in humans are included.

Findings

The first reports of HPP were published by two independent groups of investigators in 1985–1986 (1,2). Signs initially attributed to HPP were periodic attacks of muscle fasciculation, spasm, weakness, and recumbency, accompanied by high serum potassium concentrations (1,2). Since then it has become apparent that the disease is genetic and widely disseminated, particularly among well–muscled, halter–type, quarter horses. The early case descriptions only represented the tip of a large iceberg, since it has recently been estimated that by 1989 about 0.4% of all quarter horses were affected by HPP (3). By 1992, it had become recognized that all known cases of HPP were restricted to one family of quarter horses and that all were descendants of one sire (Figure 1) (4). This sire was not named in the scientific literature, but on May 27, 1992, the University of Saskatchewan put out a news release stating that all affected horses in the university herd were descendants of the sire Impressive. Subsequently, Spier (5) confirmed that all her research horses were descendants of Impressive. Because of this familial association, the disease is sometimes referred to by horse owners as "Impressive Syndrome."

Pathophysiology of hyperkalemic periodic paralysis

Hyperkalemic periodic paralysis in horses is almost identical to some types of HPP seen in humans. There is a particularly strong resemblance to the human disease

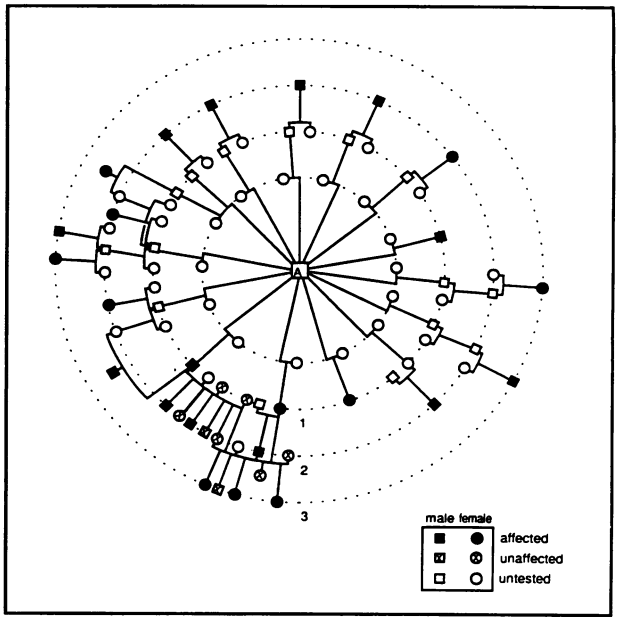

Figure 1. Interrelationship of HPP–affected horses. Note that where testing over several generations was possible, every affected horse has an affected parent (updated from reference 4).

described by Gamstorp and known as adynamia episodica hereditaria (6–8). In both human and equine HPP, there is a permanent defect in ion transport across the skeletal muscle cell membrane, resulting in increased sodium permeability, reduced polarization, and thus changes in muscle excitability (8–14). Cooling further increases the membrane potential of HPP–affected equine muscle in vitro(14), thereby making it even more excitable. It is well recognized that clinical attacks can be induced in some forms of HPP in humans by exposure to cold (7–9,13,15,16). Initially, there was confusion in the literature regarding the pathogenesis of HPP in both humans and horses as to whether the Na–K ATPase (10,12) or a sodium channel was defective (11,13,14). The balance of the physiological studies favors a primary abnormality in the sodium channel (11,13,14). This finding was confirmed by DNA sequencing, which showed that HPP is associated with certain alleles of the gene coding for the skeletal muscle sodium channel (17,18). Most recently, the change in the sodium channel in horses has been localized to a point mutation that results in a change in a single amino acid in the alpha subunit of the sodium channel protein. This change is in a highly conserved, and thus, likely a functionally important region of the protein. To date, all HPP–affected but no unaffected horses carry this abnormal sodium channel gene (19).

In humans, point mutations in the alpha–subunit of the adult human muscle, voltage–dependent, sodium channel are responsible for some types of HPP (17,20,21). In heterozygotes, only some of the channels will be defective. The sodium channel normally opens to allow rapid membrane depolarization in the initial phase of the action potential. Normal channels close once the membrane has depolarized. The defective channels fail to inactivate and remain open (11,22). This allows an excessive inward sodium current and excessive membrane depolarization (11,22). Elevations in serum potassium favor additional repetitive openings of the defective

Figure 2. Prolapse of the third eyelid in a horse udergoing a clinical attack of hyperkalemic periodic paralysis. The prolapse was intermittent.

channels and further depolarization (11,23). In heterozygotes, only some of the sodium channels will be defective. It has been postulated that the muscle cell depolarization produced by defective channels closes normal sodium channels, thus rendering them unable to generate an action potential. This mechanism would thus explain the dominant nature of the defect, because the population of aberrant channels affects the functioning of normal channels. Inactivation of sodium channels prevents the formation of an action potential and also explains weakness (22).

In equine HPP, the muscle membrane is more depolarized (less negative) than normal (14). Again this could be attributed to excessive opening of abnormal sodium channels. Muscle fasciculation and spasm, commonly seen during clinical attacks in horses, can be explained by depolarization of the membrane towards threshold by abnormal sodium channels (3). Only in severe attacks is the depolarization sufficient to inactivate normal sodium channels, thus abolishing the action potential and producing weakness. Equine HPP muscle held at room temperature is not particularly sensitive to changes in extracellular potassium (14). However, as HPP muscle behaves differently at room and body temperature, it is possible that sensitivity to extracellular potassium is increased at body temperature.

Hyperkalemia during clinical attacks of HPP (1–3,24,25) may be secondary to increased release of muscle potassium as potassium channels open to repolarize the membrane. An alternative explanation is that dietary potassium is less able to enter the myocytes and thus accumulates in the serum.

Exogenous administration of potassium is a reliable method of precipitating attacks of HPP in affected horses (3,24–26). The resultant hyperkalemia further reduces membrane polarization towards threshold, resulting in spontaneous, generalized muscle contraction and obvious clinical signs.

Clinical signs of hyperkalemic periodic paralysis

Signs of HPP are most frequently observed in two to three–year–old, well–muscled, male, show quarter horses (1,25). To date, all reported cases of HPP–affected horses have been descendants of the sire Impressive (4,5,27). This stallion is a renowned sire of halter quarter horses. He was trained for racing, but this plan had to be cancelled because of fears that the horse might hurt himself (28). Whether or not this was related to HPP is unknown. Halter horses are mainly used for showing on a lead halter and are judged partly on having a massive muscular appearance. Because this blood line is used in other breeds, HPP can also be seen in paint horses and Appaloosas (4,25). Experiments have shown that clinical attacks of HPP can be induced with equal ease in males and females. Nursing foals are more susceptible to provocation with potassium chloride than are mature horses (3). The tendency for owners to observe clinical cases in two to three–year–old males may simply be a reflection of the close observation that males raised for showing are given. In addition, stress and feeding regimes associated with showing may predispose HPP–affected horses to clinical attacks. The influence of anabolic steroids on susceptibility to attacks has not been studied. It may be worthwhile to do this since anabolics are sometimes given to this type of horse to increase muscle mass.

The factors that trigger clinical attacks are not well defined, but probably include chilling (14), transportation (3,24), recovery from anesthesia (24,29,30), and the stresses and conditioning associated with showing. It is also likely that exercise followed by poor cooling out can induce attacks in horses. In humans, hyperkalemia, weakness, and attacks of HPP can be precipitated by rest, particularly in bed, following intense exercise (9,13,15,31–35). Light exercise may abort attacks in humans (35).

Equine HPP has been confused with a wide variety of diseases, especially colic, tying up, and accidental recumbency during transportation (trailer wrecks). The initial case reports indicated that weakness and recumbency were commonly observed in attacks of HPP (1,2). This is likely why the disease is referred to as a paralysis. However, experimental studies have indicated that while recumbency may be the most dramatic sign of HPP, it is not the most common sign (3). In heterozygotes, the most common, and usually the earliest, sign seen during clinical attacks is muscle fasciculation (3). This can look like shivering or fasciculations due to pain or stress. Some horses with HPP have particularly severe fasciculations that result in gross contractions of the cutaneous musculature or uncoordinated contractions running back and forth along the body. In some horses, this may be the only sign. In more severe cases, the signs progress to spasm of various skeletal muscle groups. If the muscles of the face are affected, the lips and eyelids become retracted (risus sardonicus) and the jaws stiff. Sometimes frothy saliva drools from the lips. The third eyelid may prolapse; this usually occurs for brief periods and may be bilateral or unilateral (Figure 2). Spasm of the leg muscles can give rise to a stiff–legged gait with poor placement of the feet. The horse may subsequently become weak and recumbent. Many horses have an increased respiratory rate during attacks, and some have inspiratory stridor, due to spasm or paralysis of the laryngeal or pharyngeal muscles (3). Hyperkalemia also affects cardiac function and can produce bradycardia (36). However, there are no consistent changes in the heart rate in HPP–affected horses suffering clinical attacks of HPP (3). In rare instances, a horse will die

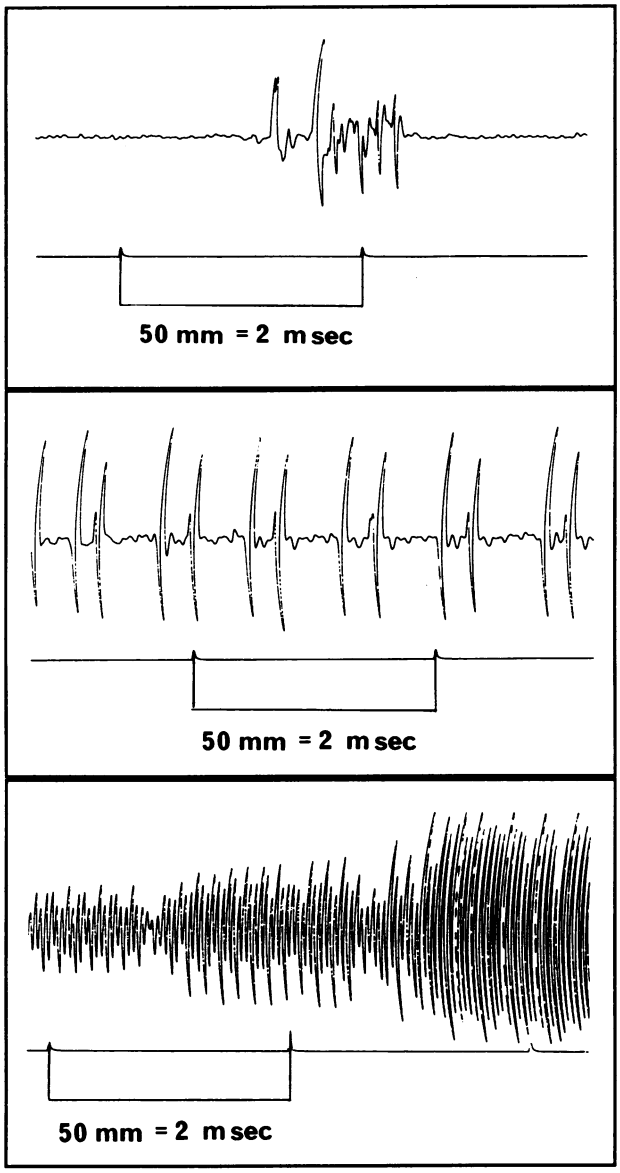

Figure 3. Electromygraphic features of normal and HPP–affected horses. Reprinted with permission from Canadian Journal of Veterinary Research (37).
a. Normal insertional activity
b. Myotonic discharges recorded in an HPP–affected horse while it was clinically normal.
c. Trains of doublets recorded in an HPP–affected horse while it was clinically normal.

during an attack, either from respiratory paralysis or cardiac failure secondary to hyperkalemia. Attacks can cease at any stage and vary in duration from a few minutes to several hours (1,3,24).

In one recent report (29), severe signs of HPP with marked and persistent dyspnea were seen at an early age due to laryngeal spasm or pharyngeal paralysis. These foals were born from matings in which both parents were from the affected line of quarter horses. Dyspnea is not consistently accompanied by hyperkalemia in these foals (29). Severe dyspnea has not been reported in foals that are known to be heterozygotes, so this suggests that homozygotes may be more severely affected.

Clinical attacks of HPP can be brief and many may be missed, particularly when horses are kept at pasture. In our research herd, clinical attacks of HPP are rarely observed (3). However, HPP–affected horses have more problems over the year than do nonaffected horses. The main problems seen are involuntary recumbency, particularly during trailering, and superficial abrasions (3). Another problem area is anesthesia. Although horses with HPP can be anesthetized successfully, there are several reports of attacks of HPP following recovery from anesthesia (24,29,30), and one horse was recumbent for a prolonged period and eventually died (30).

TABLE 2. Laboratories performing HPP gene probe testing

Veterinary Genetics Laboratory
School of Veterinary Medicine
Department of Medicine
University of California
Davis, California 95616-8737

Contact the laboratory first to get the USDA permit number for importation of blood (Fax 916 752 3556).

Dr Doug Nickel
Room 2234
Health Science Center
3330 Hospital Drive
Calgary, Alberta T2N 4N1

Send whole EDTA treated (purple top) blood by courier. It is best to collect and send the samples on the same day, at the beginning of the week. To avoid fraud check that the blood is drawn from a horse matching the description on the registration papers and include the registered name of the horse with the sample.

Diagnosis of hyperkalemic periodic paralysis

In the field, the test of choice for HPP susceptibility is the gene probe for HPP–type sodium channel DNA. This is the most sensitive test for detecting the mutation in horses susceptible to HPP. Diagnosis can also be based on clinical signs of HPP together with an elevated serum potassium concentration. This is the only method of proving the horse is suffering from clinical attacks of HPP. In order to avoid problems with spurious potassium elevations due to potassium leaking out of red cells, plasma should be separated soon after the blood has clotted.

The gene probe for the DNA that codes for the defective sodium channel requires whole anticoagulant(EDTA)–treated blood. Theoretically, the test can also be performed on other tissues obtained at necropsy. The DNA is initially extracted from the cells. It is then mixed with a probe consisting of a small complimentary DNA strand coding for HPP–type skeletal muscle sodium channels. If DNA containing the defective gene is present, the DNA hybridizes and can then be multiplied up using the polymerase chain reaction and measured. This test has only recently been developed (19). During its validation, the test correctly identified 51 HPP-affected horses (the initial diagnosis was based on potassium chloride challenge testing, or documentation of elevated serum potassium during clinical attacks, or the observation of repeated attacks of muscle fasciculation). This test is available commercially from several sources (Table 2). The gene probe is particularly

useful in prepurchase examinations and in deciding whether or not to use a particular horse for breeding.

Serum potassium is usually, but not always, elevated during attacks; concentrations can be as high as 9.6 mmol/L, but they are usually between 6 mmol/L and 8 mmol/L (3). Concentrations are only elevated during and for approximately one to two hours after the attack, so it is important to take the sample rapidly if HPP is suspected. Since potassium leaks out of red blood cells, the serum should be separated soon after the sample has clotted in order to obtain a valid result. Hemolyzed samples should not be submitted.

Other tests that have been used are the potassium chloride challenge test and electromyography (3,24,37). Electromyography requires a machine but gives an immediate result; normal horses should only give initial insertional activity. Affected horses show spontaneous discharges, including fibrillation potentials and positive waves. The most specific findings are myotonic and pseudomyotonic discharges and trains of doublets (Figure 3). In the affected line of quarter horses, doublets are 100% sensitive and specific for HPP; however, they are difficult to see without recording and playback apparatus (37). Myotonic discharges are readily detectable, because they produce a high-pitched, dive bomber sound and are 90% sensitive and specific for HPP in descendants of Impressive (3,37).

The potassium chloride challenge test involves fasting the horse for 12 h and administering an oral solution of 1% potassium chloride (KCl) in water. The horse is then monitored carefully for the next six hours. Most horses begin to show signs one to three hours after administering the solution. On a positive test, serum potassium concentrations usually rise dramatically to higher levels than in controls (3,38). Some workers report that potassium concentrations peak earlier in HPP–affected horses than in controls. However, this is probably related to the administration of treatments for HPP at the onset of signs (38). When horses are left untreated, serum potassium concentrations continue to rise and peak later than in controls (3). Potassium chloride challenge testing is very time consuming, because at least five tests must be performed to reliably detect affected horses (3). Initially, a dose of 0.1 g KCl per kg body weight (BW) is given; if the horse shows continuous muscle fasciculation at several sites or on several occasions and hyperkalemia, a positive diagnosis is recorded. If the test is negative, it must be repeated and the dose of KCl increased by 0.025 g/kg BW. This process is repeated until a dose of 0.2 g/kg BW has been given to adult horses or 0.15 g/kg BW to suckling and weanling horses (3). Because some attacks of HPP are fatal, the horse should have an intravenous catheter placed prior to starting the test and suitable drug treatment should be on hand. Unfortunately, even with these precautions the horse may die if it is affected with HPP (3).

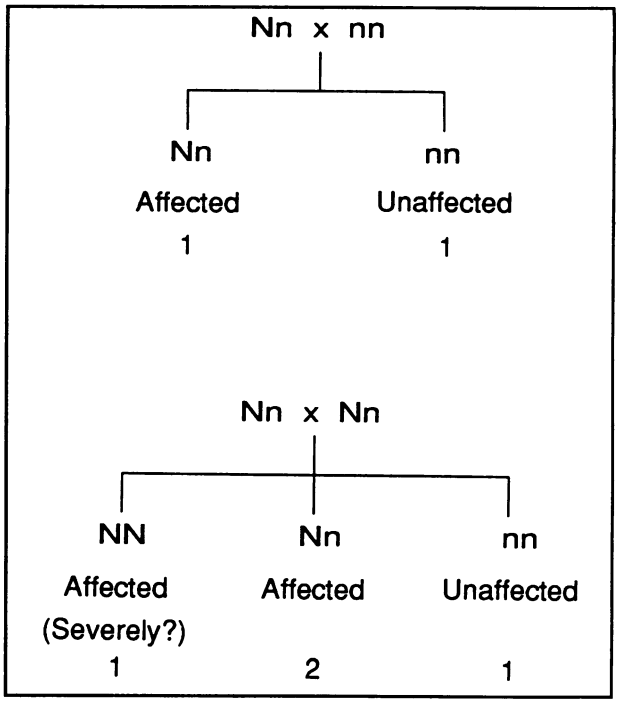

Figure 4. Predicted ratios of affected and unaffected offspring for the common matings of HPP–affected and normal parents.

Treatment

Emergency treatment during attacks usually consists of the intravenous administration of 5% dextrose (2 mL to 6 mL/kg BW), together with either sodium bicarbonate (1 mmol/kg to 2 mmol/kg BW) or calcium (0.2 mL/kg BW of 23% calcium gluconate). Calcium should be infused slowly, and it is usually mixed with the dextrose. Both dextrose and bicarbonate aid entry of potassium into the cells and thus protect the horse against the cardiotoxic effects of potassium. Calcium directly antagonizes the effects of hyperkalemia. Severely affected individuals suffering from upper airway obstruction may require an emergency tracheostomy (29).

Once an attack has occurred affected horses are usually placed on long-term treatment. This often involves reducing the dietary potassium intake. The commonly fed whole grains — oats, barley, wheat, and corn — are all relatively low in potassium. Bran, however, is moderately high in potassium (about 1.3% potassium on a dry matter basis). Protein supplements, such as canola meal (about 1.3%) and soybean meal (about 2.1%), are also rich in potassium. High potassium feeds, such as sugar beet molasses (about 6%), should be avoided. Analysis of several sources of hay can help identify a low potassium variety. Sweetfeeds that contain molasses and some electrolyte preparations may also be high in potassium. Sugar beet pulp is a good low potassium (0.2%) roughage for horses. It is also low in phosphorous (0.1%) and vitamin A (39). For adult horses, it should be fed with grain and some high quality grass hay and balanced with phosphorous and vitamin A containing supplements, as necessary. Medical treatment involves continuous administration of potassium wasting diuretics, such as acetazolamide. Acetazolamide is usually used at doses of 2 mg to 3 mg/kg BW, per os, two or three times a day (1,26). Although hydroclorthiazides have fewer side effects than acetazolamide in humans (8,35), they have not been used frequently in horses. Doses of 0.5 mg/kg BW, q12h, per os, have been used successfully in a horse (2). Whatever diuretic is used, the dose can be titrated downwards, with careful monitoring, until the lowest effective dose is found. Recently, diphenylhydantoin has been reported to be a useful

preventative. Given at 12 mg/kg to 14 mg/kg BW, q12h, per os, it reduced the incidence of signs, but not the severity of hyperkalemia, following experimental potassium chloride challenge (40). Clinical experience with its use is limited. In humans, beta–adrenergics, which stimulate the Na–K ATPase and help return potassium to the cell, are used in the treatment of HPP (31). Slow intravenous infusion of isoproterenol has been tried in the treatment of one horse, but therapy had to be discontinued because of tachycardia and premature ventricular contractions (30).

Genetics

Hyperkalemic periodic paralysis is a genetic disease that is inherited as an autosomal dominant trait (3,6,19,38,41). This means that heterozygotes have the potential to manifest HPP. One feature of this type of genetic transmission is that every affected individual has at least one affected parent. The suggestion that offspring of double bred horses are more severely affected indicates that the condition may be expressed to a greater degree in the homozygote. There are insufficient data at present to be sure whether or not HPP is a simple dominant condition or a codominant condition. In addition, the degree of penetrance of the gene has not been fully explored. In autosomal dominant conditions, mating an unaffected (nn) with a heterozygous affected horse (Nn) results in half of the offspring being normal(nn) and half of the offspring being affected (Nn); there is no sex predilection. If both parents are unaffected (nn), then all of the offspring are unaffected (nn). If both parents are heterozygous-affected (Nn), then one quarter of the offspring will be normal (nn), one half heterozygous-affected (Nn), and one quarter homozygous-affected (NN) (Figure 4).

Selection

Impressive, the foundation sire for HPP, was born on April 15, 1969. Twenty years later the ancestry of over 2% of all registered quarter horses, 55,521 in all, could be traced to this sire. Assuming no selection, the number of HPP–affected quarter horses can be calculated as half the first generation, a quarter of the second generation, and so on. These calculations indicate that by 1989, about 0.4% of the breed would have been affected. Unfortunately, a number of lines of evidence suggest that there has been active selection for HPP–affected horses. The affected line has grown rapidly and breeding farms preferentially use HPP–affected stock (41). Assuming only HPP–affected horses were used for breeding, a maximum of 1% of the breed, or 25,000 horses, would have been affected with HPP by 1989. Today, more horses are likely to be affected due to the popularity of this line of horses.

An important question is, Why would a genetic disease be selected for? It has been said that breeds get the disease they deserve. Show halter quarter horses are selected for a muscular appearance, and HPP probably helps to produce this appearance. Electrophysiological measurements show that the muscles of HPP-affected horses are frequently contracting spontaneously (24,37). This is likely to lead to muscle hypertrophy. A slight increase in serum creatinine has been reported in some HPP–affected horses (1). We speculate that this may be due to increased release of creatine from a greater muscle mass.

Conclusions

Veterinarians are likely to be involved with HPP-affected horses in several different situations. Dealing with a clinically affected horse should be straightforward, providing one is aware of the symptomatology and treatment of this recently documented disease. Problems are likely to be encountered in prepurchase examinations of quarter horses, paint horses, and Appaloosas. Affected horses usually appear clinically normal and yet the presence of HPP has major adverse implications for breeding, insurance, and, possibly, for strenuous performance. Hyperkalemic periodic paralysis status can be determined by having whole blood containing EDTA as an anticoagulant tested with a gene probe. Because these tests are costly, they should usually be limited to descendants of Impressive. Hyperkalemic periodic paralysis has not been confirmed in other than Impressive descended horses, so these need not be routinely tested. Hyperkalemic periodic paralysis is found in horses many generations removed from Impressive, so it is important that the pedigree be known for at least six generations to detect Impressive ancestry. If an immediate result is required, for example because the horse is to be anesthetized, electromyography gives an immediate and 90% reliable indication of HPP status.

Breeders and showers of halter type horses are going to be in a particularly difficult position. Hyperkalemic periodic paralysis affected horses may do better in shows, and some owners will have a considerable investment in individual horses. The long–term health of the breed and the common good, however, suggest that HPP–affected horses be removed from the breeding pool. If only nonaffected horses are used for breeding, no HPP–affected offspring will be produced. There is also a good case for selecting against HPP at halter shows. This could be accomplished by compulsory testing at halter shows and by reevaluating judging criteria to favor less muscular horses in halter classes.

Hyperkalemic periodic paralysis has been publicly recognized for about seven years, and during this time, perception has changed from regarding the condition as a novelty to considering it an important genetic disease. Without prompt action, inbreeding will produce more homozygous affected individuals and the indications are that this may greatly increase the expression of serious clinical disease. Veterinarians can play an important role in testing suspect horses and in educating the public about this condition. CVJ

References

1. Cox JH. An episodic weakness in four horses associated with intermittent serum hyperkalemia and the similarity of the disease to hyperkalemic periodic paresis in man. Proc Am Assoc Equine Practitioners 1985; 21: 383–391.
2. Steiss JE, Naylor JM. Episodic muscle tremors in a quarter horse: Resemblance to hyperkalemic periodic paralysis. Can Vet J 1986; 27: 332–335.
3. Naylor JM, Jones V, Berry S-L. Clinical syndrome and diagnosis of hyperkalemic periodic paralysis in Quarter Horses. Equine Vet J 1993; 25: 227–232.
4. Naylor JM, Robinson JA, Bertone J. Familial incidence of equine hyperkalemic periodic paralysis in Quarter Horses. J Am Vet Med Assoc 1992; 200: 340–343.

5. Moore J. Umasking the fatal flaw. Equus 1993; 185: 44–50, 80–85.
6. Gamstorp I. Disorders characterized by spontaneous attacks of weakness connected with changes of serum potassium. Prog Clin Biol Res 1989; 306: 175–195.
7. Riggs JE. Review. Periodic paralysis. Clin Neuropharmacol 1989; 12: 249–257.
8. Gamstorp I, Hauge M, Helweg-Larsen HF, Mjones H. Adynamia episodica hereditaria. A disease clinically resembling familial periodic paralysis but characterized by increasing serum potassium during the paralytic attacks. Am J Med 1957; 23: 385–390.
9. Ballanyi K, Grafe P. Changes in intracellular ion activities induced by adrenaline in human and rat skeletal muscle. Pflugers Arch 1988; 411: 283–288.
10. Spier SJ, Carlson GP, Pickar J, Snyder JR. Hyperkalemic periodic paresis in horses. Proc Am Coll Vet Int Med 1989; 7: 499–500.
11. Cannon SC, Brown RH Jr, Corey DP. A sodium channel defect in hyperkalemic periodic paralysis; potassium-induced failure of inactivation. Neuron 1991; 6: 619–626.
12. Lehmann-Horn F, Rudel R, Ricker K, Lorkovic H, Dengler R, Hopf HC. Two cases of adynamia episodica hereditaria: in vitro investigation of muscle cell membrane and contraction parameters. Muscle Nerve 1983; 6: 113–121.
13. Bradley WG. Adynamia episodica hereditaria. Clinical, pathological and electrophysiological studies in an affected family. Brain 1969; 92: 345–378.
14. Pickar JG, Spier SJ, Snyder JR, Carlsen RC. Altered ionic permeability in skeletal muscle from horses with hyperkalemic periodic paralysis. Am J Physiol 1991; 260: C926–C933.
15. Carson MJ, Pearson CM. Familial hyperkalemic periodic paralysis with myotonic features. J Pediatr 1964; 64: 853–865.
16. Subramony SH, Wee AS, Mishra SK. Lack of cold sensitivity in hyperkalemic periodic paralysis. Muscle Nerve 1986; 9: 700–703.
17. Fontaine B, Khurana TS, Hoffman EP, *et al.* Hyperkalemic periodic paralysis and the adult muscle sodium channel-subunit gene. Science 1990; 250: 1000–1002.
18. Rudolph JA, Spier SJ, Byrns G, Hoffman EP. Linkage of hyperkalemic periodic paralysis in Quarter horse to the adult skeletal muscle sodium channel gene. Anim Genet 1992; 23: 241–250.
19. Rudolph JA, Spier SJ, Byrns G, Rojas CV, Bernoco D, Hoffman EP. Periodic paralysis in Quarter Horses: a sodium channel mutation disseminated by selective breeding. Nature Genet 1992; 2: 144–147.
20. Ptacek LJ, George AL Jr, Griggs RC, *et al.* Identification of a mutation in the gene causing hyperkalemic periodic paralysis. Cell 1991; 67: 1021–1027.
21. Rojas CV, Wang JZ, Schwartz LS, Hoffman EP, Powell BR, Brown RH Jr. A Met-to-Val mutation in the skeletal muscle Na+ channel alpha-subunit in hyperkalemic periodic paralysis. Nature 1991; 354: 357–389.
22. Lehmann-Horn F, Iaizzo PA, Hatt H, Franke C. Altered gating and conductance of Na+ channels in hyperkalemic periodic paralysis. Pflugers Arch 1991; 418: 297–299.
23. Ricker K, Camacho LN, Grafe P, Lehman-Horn F, Rudel R. Adynamia episodica hereditaria: what causes the weakness? Muscle Nerve 1989; 12:883–891.
24. Spier SJ, Carlson GP, Holliday TA, Cardinet GH III, Pickar JG. Hyperkalemic periodic paralysis in horses. J Am Vet Med Assoc 1990; 197: 1009–1017.
25. Cox JH, DeBowes RM. Episodic weakness caused by hyperkalemic periodic paralysis in horses. Compend Contin Educ Pract Vet 1990; 12: 83–88.
26. Cox JH, De Bowes RM, Boyer JE Jr. Response of normal and acetazolamide treated horses to oral potassium chloride challenge. Proc Am Coll Vet Med 1988; 6: 728.
27. Naylor JM. Equine hyperkalemic periodic paralysis. Proc Am Coll Vet Int Med 1992; 10: 390–393.
28. Chamberlain R. Impressive. Am Quarter Horse Assoc 1985: 146–151.
29. Traub-Dargatz JL, Ingram JT, Stashak TS, *et al.* Respiratory stridor associated with polymyopathy suspected to be hyperkalemic periodic paralysis in four Quarter Horse foals. J Am Vet Med Assoc 1992; 201: 85–89.
30. Robertson SA, Green SL, Carter SW, Bolon BN, Brown MP, Shields RP. Postanesthetic recumbency associated with hyperkalemic periodic paralysis in a Quarter Horse. J Am Vet Med Assoc 1992; 201: 1209–1212.
31. Bendheim PE, Reale EO, Berg BO. Beta adrenergic treatment of hyperkalemic periodic paralysis. Neurology 1985; 35: 746–749.
32. McManis PG, Lambert EH, Daube JR. The exercise test in periodic paralysis. Muscle Nerve 1986; 9: 704–710.
33. Ricker K, Rohkamm R, Bohlen R. Adynamia episodica and paralysis periodica paramyotonica. Neurology 1986; 36: 682–686.
34. Subramony SH, Wee AS. Exercise and rest in hyperkalemic periodic paralysis. Neurology 1986; 36: 173–177.
35. Lewis ED, Griggs RC, Moxley RT. Regulation of plasma potassium in hyperkalemic periodic paresis. Neurology 1979; 29: 1131–1137.
36. Castex A-M, Bertone JJ. ECG of the Month. J Am Vet Med Assoc 1989; 194: 654–655.
37. Robinson JA, Naylor JM, Crichlow EC. Use of electromyography for the diagnosis of equine hyperkalemic periodic paresis. Can J Vet Res 1990; 54: 495–500.
38. Spier SJ, Carlson GP, Harrold D, Bowling A, Byrns G, Bernoco D. Genetic studies of hyperkalemic periodic paralysis in horses. J Am Vet Med Assoc 1993; 202: 933–937.
39. Hintz HF. Feeds for livestock. In: Naylor JM, Ralston SL, eds. Large Animal Clinical Nutrition. St Louis: Mosby Year Book, 1991: 120–130.
40. Beech J, Fletcher JE, Tripolitis L, Lindborgh S. Effects of phenytoin in two myotonic horses with hyperkalemic periodic paralysis. Muscle Nerve 1992; 15: 932–936.
41. Naylor JM, Robinson JA, Crichlow EC, Steiss JE. Inheritance of myotonic discharges in American quarter horses and the relationship to hyperkalemic periodic paralysis. Can J Vet Res 1992; 56: 62–66.