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Review

A review of equine muscle disorders

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Abstract

Muscle disorders are a common cause of disability in horses. For many years, clinical manifestations such as muscle pain, exercise intolerance, weakness, and stiffness were believed to be caused by a single syndrome. However, in the past years a broad spectrum of muscle disorders have been recognized including glycogen and polysaccharide storage myopathies, malignant hyperthermia, mitochondrial myopathy, hyperkalemic periodic paralysis and others. For some, a specific mutation has been identified. Recognition of the myopathic clinical phenotype and thorough clinical, electrodiagnostic, and histological evaluations are essential to further our understanding of equine myopathies. Advances in understanding equine myopathies may potentially benefit other species including humans.

Keywords: Equine; Exertional; Myopathy; Myotonia; Rhabdomyolysis

1. Introduction

Muscle disorders are a common cause of disability in affected horses, and in the past, have been known by several names including tying up, Monday morning disease, azoturia, equine rhabdomyolysis, and equine myoglobinuria. Although originally thought to be a single clinical syndrome, it is now clear that these clinical manifestations are common to several different muscle disorders with different etiologies [1]. In 1992 the first hereditary muscle disease, hyperkalemic periodic paralysis in Quarter Horses, was reported [2,3] and a genetic test is available for diagnosis. Recently metabolic, inflammatory, dystrophic and other inherited muscle diseases have been described in horses [4–10]. A specific genetic defect and mode of inheritance have only been identified in hyperkalemic periodic paralysis [3], glycogen branching enzyme deficiency [7], and malignant hyperthermia [8].

Horses have a number of muscle disorders which share similar clinical, histopathological and in some cases molecular features with humans. Thus the horse can be considered as an animal model for human muscle diseases. Disorders that affect horses and man include equine motor neuron disease [11] with many similarities to human amyotrophic lateral sclerosis [12], malignant hyperthermia in Quarter Horses with a mutation in the calcium release channel of the skeletal muscle sarcoplasmic reticulum, *RyR1* gene [8], hyperkalemic periodic paralysis in Quarter Horses caused by a mutation in the α-subunit of the skeletal muscle sodium channel, *SCN4A* gene [2], and glycogen branching enzyme 1 deficiency in Quarter Horse and Paint foals due to a mutation in the glycogen branching enzyme 1, *GBE1* gene [7]. With increased recognition of the myopathic phenotype in horses by veterinarians, and use of state-of-the-art histological, biochemical and molecular techniques, the spectrum of myopathies affecting the horse will be greatly expanded.

Known causes of equine myopathies are shown in Table 1. This classification separates myopathies into non-exertional and exertional categories. These categories are further divided into whether or not they are associated with rhabdomyolysis. A final category covers diseases associated with altered membrane conduction. This review highlights the most important recognized muscle disorders in horses with an emphasis on inherited, metabolic, toxic, and inflammatory myopathies.

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Table 1
Classification of myopathies in horses

I. Non-exertional myopathies	II. Exertional myopathies
A. Rhabdomyolysis	*A. Rhabdomyolysis*
Nutritional	Sporadic
Vitamin E/selenium deficiency	Lack of training
Metabolic	Overexertion
Glycogen branching enzyme deficiency	Heat exhaustion
Polysaccharide storage myopathy	Electrolyte imbalances
Anesthesia associated	Chronic
Compartmental myopathy	Dietary imbalances
Malignant hyperthermia	Polysaccharide storage myopathy
Toxic	Recurrent exertional rhabdomyolysis
Pasture associated	Idiopathic
Drug/chemical associated	Trauma
Ionophore toxicosis	
Organophosphate toxicity	*B. No rhabdomyolysis*
Trauma	Mitochondrial myopathy
Inflammatory	Complex I respiratory chain enzyme deficiency
Infectious	Pituitary pars intermedia dysfunction myopathy
Viral, bacterial, parasitic	
Immune-mediated	III. Altered muscle membrane conduction
B. No rhabdomyolysis	Electrolyte abnormalities
Pituitary pars intermedia dysfunction myopathy	Tetany (severe hypocalcemia)
Steroid induced	Others
Disuse atrophy	Hyperkalemic periodic paralysis
Muscle wasting associated with neoplasia	Myotonic dystrophy
Neoplasia (rare)	Tick myotonia (ear tick: *Otobius megnini*)

2. Non-exertional myopathies with rhabdomyolysis

2.1. Selenium/vitamin E deficiency

Nutritional myodegeneration (also known as nutritional muscular dystrophy, dystrophic myodegeneration, nutritional myodystrophy, or white muscle disease) is a peracute to subacute myodegenerative disease of cardiac and skeletal muscle caused by a dietary deficiency of selenium and to a lesser extent vitamin E (α-tocopherol) [13]. Clinical manifestations occur mainly in young growing foals but can also occur in older horses. Selenium functions as a redox element and is a component of at least 35 selenoproteins including glutathione peroxidase, thioredoxin reductase, iodothyronine deionidases, and selenoprotein P [14]. Selenium and vitamin E serve as biological antioxidants and prevent cellular damage from reactive oxygen species resulting from normal cellular metabolism. Rapidly growing or heavily fertilized plants, and legumes tend to be low in selenium. Plants grown in poorly aerated, acid soils, soils originated from volcanic rock, or soils with a high content of iron or sulfur have less selenium. Sulfur-containing fertilizers contribute to selenium deficiency, since sulfur inhibits selenium uptake by plants and absorption in animals. In addition, pelleted diets may be deficient in these two antioxidants. Vitamin E and selenium deficiency can also be identified in neonatal foals born from deficient mares [15]. In humans, insufficient selenium intake, malabsorption, and conditions associated with chronic oxidative stress have been implicated in myopathies due to selenium deficiency [16].

Peracute clinical signs in deficient foals include recumbency, tachypnea, dyspnea, myalgia, arrhythmias, and sudden death. In the subacute form, foals may show severe weakness, inability to stand, muscle fasciculations, firm muscles on palpation, stiffness, stilted gait, myalgia, lethargy, dysphagia, trismus, ptyalism, and weak suckle reflex [15]. Failure of passive transfer, aspiration pneumonia, and starvation are common complications. Important laboratory alterations include markedly elevated serum creatine kinase (CK) and aspartate aminotransferase (AST) activities, hyperproteinemia, azotemia, hyponatremia, hypochloremia, hyperkalemia, hyperphosphatemia, respiratory acidosis, and myoglobinuria [17]. Whole blood selenium and glutathione peroxidase activity, and in some cases plasma vitamin E concentrations, are low. Grossly the muscle is pale with white streaks representing coagulative necrosis and edema (Fig. 1). Commonly affected muscles include myocardium, thoracic, pelvic and cervical muscles, diaphragm, tongue, pharynx, intercostals and masticatory muscles [15,18]. Histological features include myonecrosis and regeneration with histiocytic infiltration, fibrosis and calcification in chronic cases [15]. Treatment consists of supportive therapy, prevention of complications, and supplementation of vitamin E and selenium.

2.2. Metabolic myopathies: glycogenoses

Glycogenoses are a group of diseases characterized by abnormal storage of glycogen in tissues [19]. Both lysosomal and non-lysosomal glycogenoses have been described in humans [19]. In horses, two glycogenoses have

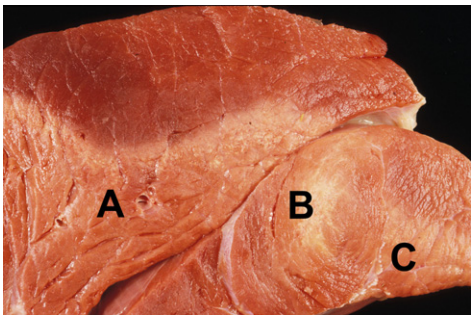

Fig. 1. Nutritional myodegeneration. Note severe muscle pallor, white streaks (A and B), and edema (B) in semimembranosus and semitendinosus muscles of affected horse.

been reported; glycogen branching enzyme deficiency (GBED) or glycogenosis type IV [7], and polysaccharide storage myopathy (PSSM) [6].

2.2.1. Glycogen branching enzyme deficiency

Glycogen branching enzyme deficiency is a fatal autosomal-recessive disease of Quarter Horses and Paint Horses caused by Y34X missense mutation at codon 34 in exon 1 (C to A substitution at position 102 of coding sequence) of the glycogen branching enzyme 1 (*GBE1*) gene [7]. This mutation introduces a premature stop codon and dramatically decreases the amount of GBE protein in homozygotes. Carriers of this mutation trace back to two prominent founders of Quarter Horse breeds. Approximately 8% of Quarter Horses and Paint Horses are carriers of GBED [20]. Affected foals have extremely low glycogen branching enzyme activity, and no measurable reactivity for the enzyme on Western blot; therefore, diseased foals cannot store and mobilize glycogen to maintain normal glucose homeostasis [21].

Common clinical signs of GBED include abortion of the affected fetus and stillbirths; it is invariably fatal in foals [21,22]. Clinical signs in neonates vary but include hypoglycemia, hypothermia, progressive muscle weakness, inability to rise, collapse, seizures, flexural limb deformities, respiratory failure, and death [21]. Common laboratory findings include leukopenia, intermittent hypoglycemia, and moderate elevations of serum CK, AST, and gamma glutamyl transferase activities [21]. Histologically, there is decreased periodic acid Schiff (PAS) background staining and accumulation of amorphous globular and crystalline inclusions in skeletal muscle [21]. Abnormal polysaccharide in skeletal muscle may not always be present in feti but cardiac Purkinje fibers appear to consistently contain amorphous PAS-positive globular inclusions in affected foals [21]. Abnormal polysaccharide can be identified in cardiac myofibers (Fig. 2), neural tissue and observed inconsistently in the liver of foals older than 4 weeks of age. Ultrastructurally, these inclusions appear spherical and filamentous with few normal β-glycogen particles [21]. Nursing care has prolonged life in affected foals, but unfortunately there is no curative treatment.

2.2.2. Polysaccharide storage myopathy

Polysaccharide storage myopathy was first described in Quarter Horse-related breeds by Valberg in 1992 [6]. The disease is characterized by high glycogen and glucose-6-phosphate in skeletal muscle as well as abnormal accumulations of complex polysaccharide inclusions [6,23]. A recent review of muscle biopsies from horses with suspected neuromuscular disease submitted to a diagnostic laboratory identified PSSM in 40% of the horses [24]. Although more than 50 breeds were included in this review, this study and others support that Quarter Horses and related breeds (Paints and Appaloosas), draught horses (mainly Belgians and Percherons), and Warmbloods are the most common affected breeds [25–27]. However, a form of this disease has been reported in Thoroughbreds, Morgans, Andalusians, Arabians, Standardbreds, and others but in low numbers [24,28]. Limited breeding trials and pedigree analysis in Quarter Horses indicate an autosomal-dominant mode of inheritance in this breed [29]. The prevalence of the disease in this breed has been estimated to be 6–12% with higher incidence in certain blood lines [25]. Belgian draught horses have a prevalence of PSSM of 36% [26].

Sporadic or episodic rhabdomyolysis (exertional and non-exertional), exercise intolerance, weakness, stiffness, muscle fasciculations, myalgia, gait abnormalities, back pain, and muscle atrophy are common clinical signs. However, horses may appear normal. Lack of regular exercise or prolonged periods of rest followed by exercise are known triggering factors of rhabdomyolysis [30]. Elevations of serum CK activity in association with exercise are common, but persistent elevations may occur at rest [26]. Muscle enzymes are often within reference values in draught and Warmblood horses [26].

Recently a whole genome association analysis identified a chromosomal region associated with PSSM in Quarter Horses. However, until a genetic test for PSSM is commercially available; the gold standard for diagnosis of PSSM is the presence of PAS-positive inclusions in muscle biopsies that are resistant to amylase digestion (Fig. 3) [24]. These inclusions are composed of β-glycogen with a less branched structure interspersed among arrays of filamentous material [6,23]. The inclusions have been observed in up to 30% of types 2A and B myofibers and often concentrated in perifascicular locations [6,23]. However, inclusions may not be

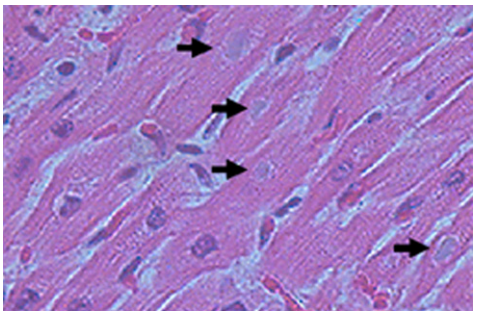

Fig. 2. Glycogen branching enzyme 1 deficiency. Formalin-fixed H&E stain at 40× of cardiac muscle from affected foal. Globular intrasarcoplasmic inclusions (arrows) are present within several cardiac myofibers.

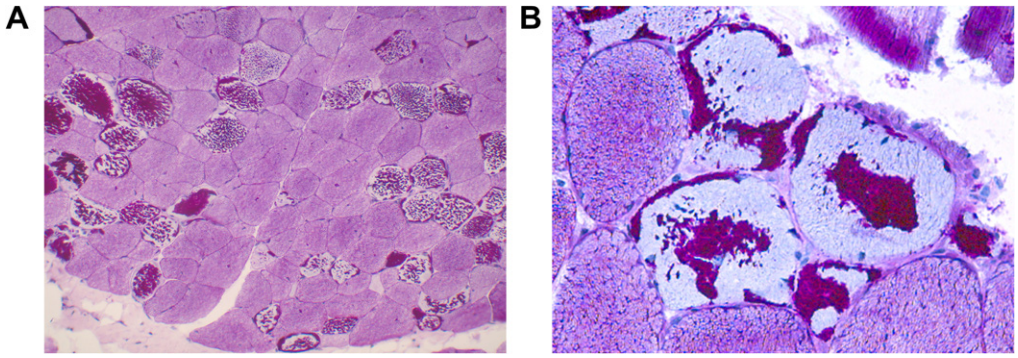

Fig. 3. Polysaccharide storage myopathy. Fresh-frozen PAS stain of a cross-section of gluteus medius muscle showing PAS-positive granular myoplasmic inclusions at 4× (A), and PAS-positive large myoplasmic inclusions at 25× (B). Both, PAS-positive material (A and B) were amylase resistant (not shown).

noted until 15 months of age [29]. While it is accepted that the presence of PAS amylase-resistant inclusions is definitive for the diagnosis of PSSM; other authors have also proposed the presence of amylase-sensitive subsarcolemmal glycogen aggregates and amylase-sensitive cytoplasmic central bodies containing glycogen with or without amylase-resistant polysaccharide to be diagnostic for the disease [31]. This diagnostic criterium has resulted in a higher prevalence of PSSM in the equine population than that reported by others, both within specific breeds and in the range of affected breeds.

Studies by Valberg and collaborators have shown that affected horses benefit from a combination of daily regular exercise, free exercise on pasture, and dietary modification that includes high-fat (13%) and low starch (<10%) content of daily digestible energy [30]. However, some gait abnormalities may not resolve.

2.3. Anesthesia associated myopathies: malignant hyperthermia

Malignant hyperthermia (MH) is a life-threatening pharmaco-genetic disease of skeletal muscle elicited by exposure to volatile anesthetics such as halothane, depolarizing muscle relaxants such as succinylcholine, and stress [32]. Mutations in the *RyR1* gene cause dysfunction of the calcium release channel of the sarcoplasmic reticulum in skeletal muscle, resulting in excessive release of calcium into the myoplasm and a hypermetabolic state characterized by intense heat, hypercapnea, lactic acidosis, and in many cases, death [32]. Following the introduction of inhalation anesthesia in horses in the 1960s, cases of MH have been suspected but seldom reported [33]. MH in horses has been triggered by halothane alone, or in combination with succinylcholine, caffeine or nerve stimulation. There is no apparent breed, gender or age predisposition in horses [34]. The most common clinical signs of MH in horses include hyperthermia that may exceed 43 °C, profuse sweating, tachycardia, tachypnea, arrhythmias, muscle rigidity, prolapse of the third eyelid, muscle contractions, rhabdomyolysis, myoglobinuria, and death with peracute rigor mortis (Fig. 4A) [34]. Since clinical manifestations of MH are triggered by pharmacological agents, diagnosis prior to anesthesia is difficult. Clinicopathological abnormalities include hypercapnea, acidosis, hypertension, electrolyte disorders, increased serum CK activities, and myoglobinuria [34]. Elevations of muscle enzymes may not be observed in cases of peracute death. No specific histochemical abnormalities have been found in muscle biopsies from affected horses [8].

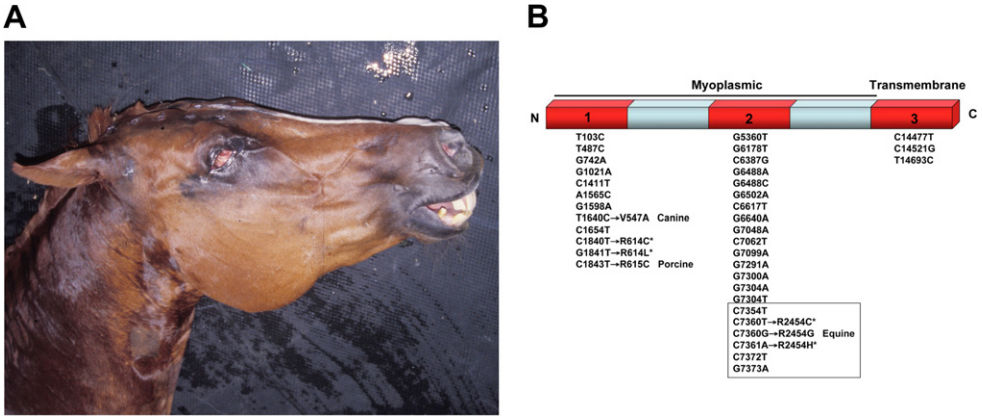

Fig. 4. Malignant hyperthermia. (A) Horse that died of a MH episode; note trismus, flared nostrils, contracted masseters, third eyelid prolapse, ocular retraction, retracted pinnae (ears pointing back), and profound sweating. (B) Ryanodine receptor 1 mRNA showing various mutations in humans clustered in three regions indicated by numbers on dark bars. Specific mutations for canine, equine, and porcine are indicated. Arrows indicate the amino acid substitution, and (*) indicate the equivalent mutation in humans. Mutations of exon 46 are indicated within the box.

Six distinct loci for malignant hyperthermia susceptibility (MHS) in humans have been identified (MHS1 to MHS6) [35]. Mutations in *RyR1* gene causing or associated with the disease have also been reported in pigs [36], dogs [37], and horses [8] (Fig. 4B). In humans and dogs, the mutations have an autosomal-dominant pattern of inheritance, while in pigs MH is an autosomal-recessive trait. Genetic evaluation of some of the parents of affected horses, and development of clinical signs under anesthesia suggest a dominant trait [8]. In three Quarter Horses, a C7360G missense mutation that generates a R2454G amino acid substitution was found [8].

Mutations in the *RyR1* gene have been implicated in central core disease and multiminicore disease [38]. There is one report of a 10-month-old pony foal with stiff gait, flexural limb deformities, and moderate hypotonia since birth that showed central cores devoid of oxidative activity in muscle biopsies; resembling those of central core disease in humans [39]. Its association with *RyR1* gene is unknown.

2.4. Toxic myopathies

Atypical myopathy or myoglobinuria of unknown etiology is a sporadic frequently fatal myopathy that occurs in grazing horses and ponies. The first report of the disease was made in 1939 in the North of Wales, Great Britain [40]. Since then, reports of outbreaks have been made in several European countries [41,42] with similar reports in Australia, Canada and United States [43–45]. This myopathy seems to have a seasonal occurrence with most cases observed in the fall [41,42]. Inclement weather including cold, humidity, and rain prior to the onset of clinical signs is a common feature [41,43]. Most horses have been at pasture for weeks to months. Isolated cases or several horses in a group can be affected. Young horses, months to few years of age (median age of 2 years), are predominantly affected [41,42].

Affected horses are generally in good body condition at the onset of clinical signs. Clinical signs include non-exercise associated sudden onset of weakness, tachycardia, muscle fasciculations, pain, myoglobinuria, sweating, full bladder on rectal palpation, reluctance to move and stiffness that rapidly progresses to recumbency and death within 3–72 h [41–43]. Dyspnea, tachypnea and respiratory distress are often reported and thought to be due to severe peracute myodegeneration of intercostal muscles, cardiac muscle and diaphragm.

Characteristic clinical laboratory abnormalities include profound elevations of serum CK (>100,000 IU/L), aspartate aminotransferase and lactate dehydrogenase, and myoglobinuria [41,42]. Large areas of muscle necrosis more severe in respiratory, postural and cardiac muscles are observed at necropsy [41]. Zenker degeneration and myonecrosis affecting predominantly type 1 fibers are the most common myopathic alterations in muscle biopsies [41]. In addition, alterations in mitochondria and sarcoplasmic lipidosis are characteristic ultrastructural features [41]. The mortality rate has been estimated to be 89% despite therapy due to respiratory failure and cardiac damage. Only a few surviving horses will fully recover and regain previous levels of physical activity. A similar seasonal pasture myopathy with a high mortality was reported in the Midwestern United States [45].

2.5. Inflammatory and necrotizing myopathies

The most common inflammatory myopathies (IM) in humans include immune-mediated dermatomyositis, polymyositis, and inclusion body myositis [46]. In horses, IMs are a result of immune-mediated and infectious causes. Based on clinical presentation and immunohistochemical evaluation, there are three distinct immune-mediated myopathies in horses that are characterized by acute severe rhabdomyolysis, severe vasculitis with infarction, and rapid muscle atrophy [5,47,48]. Infectious causes include clostridial, streptococcal, and parasitic myositis [48,49].

2.5.1. Streptococcal acute severe rhabdomyolysis

Severe acute rhabdomyolysis is a rare but often fatal complication following upper respiratory infection with *Streptococcus equi equi*, a β-hemolytic Lancefield group C streptococcus. Myalgia, myoglobinuria, stiffness, stilted gait most notably of the pelvic limbs, severe swelling and pitting edema of the epaxial and gluteal muscles, and recumbency are common clinical signs [47]. Clinical signs progress rapidly and may result in death despite aggressive antimicrobial, anti-inflammatory, fluid, and supportive therapy. The severity and rapid progression of illness in these horses resembles streptococcal toxic shock syndrome in humans, characterized by deep-tissue infection, bacteremia, sepsis, vascular collapse, and organ failure [50]. Affected horses have leukocytosis with neutrophilia, and hyperfibrinogemia. The serum CK activity is markedly elevated (>100,000 IU/L). Myonecrosis of up to 75% of myofibers with histiocytic infiltration is the most common pathological alteration in muscle biopsy samples [47]. Scattered lymphocytes may also be observed [47]. Staining with Lancefield group C carbohydrate-specific and *S. equi* M protein (SeM) specific antisera have revealed numerous cocci in skeletal muscle [47]. In addition, affected horses have elevated serum antibody titers to *S. equi* myosin binding protein [47]. The pathophysiology of the disease is not fully understood but the presence of streptococcal superantigens may play an important role as described in humans with streptococcal necrotizing myopathy [51].

2.5.2. Infarctive purpura hemorrhagica

Purpura hemorrhagica is a non-contagious disease of horses characterized by vasculitis leading to extensive edema and hemorrhage of the mucosa and subcutaneous tissue. The disease has been recognized as a sequela to infection or exposure to *Streptococcus equi equi*, *Strepococcus equi zooepidemicus*, *Rhodococcus equi*, *Corynebacterium pseudotuberculosis* and vaccination against *S. equi equi* [52]. An infarctive form of purpura hemorrhagica occurs in

horses that resembles Henoch-Schonlein purpura in humans [53]. Young to middle-aged horses are commonly affected [52]. Clinical signs develop acutely within 2–4 weeks following a respiratory infection. The most common myopathic signs include muscle swelling and stiffness with elevated muscle enzyme activities (CK > 50,000 IU/L and AST > 1000 IU/L) [48,52]. In addition, there is well demarcated subcutaneous edema of all four limbs, lethargy, anorexia, hemorrhages on mucous membranes, fever and tachycardia [52]. Neutrophilia with left shift, hypoalbuminemia, and abnormal clotting parameters are common alterations. Horses have high titers for antibodies against *S. equi* M protein by ELISA. Histologically, there is severe, multifocal coagulative necrosis of skeletal muscle. Inflammatory cells consist primarily of degenerate neutrophils, lymphocytes, plasma cells, and macrophages. Several other tissues (lungs, liver, intestines) show hemorrhages and leukoclastic vasculitis that progress to infarction [48]. The mortality rate for horses with purpura hemorrhagica was reported to be 7.5% in a retrospective study [52]. However, fatalities are high in horses with the infarctive form [48].

2.5.3. Immune-mediated myositis

Immune-mediated myositis (IMM) in horses is characterized by rapid muscle wasting, lethargy, stiffness, weakness, and fever (Fig. 5A) [5]. Muscles of the dorsal thoracolumbar area are particularly severely atrophied. Forty percent of affected horses have a history of an infection within 2 months [5]. Any breed may be affected; however, Quarter Horses appear to be over represented [5]. A bimodal age distribution has been observed with primarily horses younger than 8 years or older than 17 years of age.

The main histopathological features on muscle biopsies are histiocytic and lymphocytic infiltration of myocytes and perivascular cuffing (Fig. 5B and C) [5]. The lymphocytic infiltrate mainly consists of CD4+ cells (Fig. 5D). However, small numbers of B cells, plasma cells, and CD8+ cells are found in areas with profound inflammation. This differs from immune-mediated polymyositis in humans and dogs in which CD8+ T cells are present in greater numbers than CD4+ T cells [54–56]. There are, however, immunopathogenic similarities to canine masticatory muscle myositis [56].

Affected horses recover muscle mass within weeks to months. Long-term sequelae include focal muscle atrophy or recurrence of clinical signs. Early corticosteroid therapy has resulted in rapid improvement of clinical signs. However, horses may regain their muscle mass within months without steroid treatment [5]. This also differs from dogs with immune-mediated myopathies, as progression of muscle atrophy is inevitable unless immunosuppressive therapy is used [55,56].

3. Non-exertional myopathies without rhabdomyolysis

3.1. Pituitary pars intermedia dysfunction myopathy (Cushing's disease)

Pituitary pars intermedia dysfunction (PPID) is commonly referred as equine Cushing's disease and affects

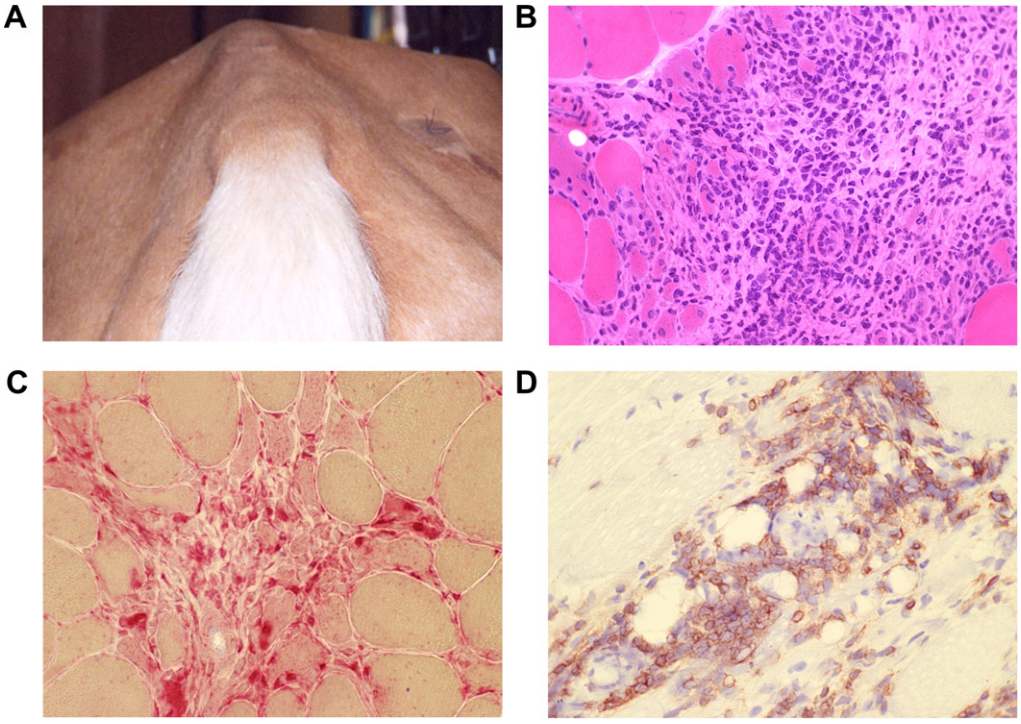

Fig. 5. Immune-mediated myositis. (A) Diseased horse with profound muscle loss. Gluteus medius muscle of this horse at 40× (B and C). (B) Fresh-frozen H&E stain showing endomysial, perimysial, and perivascular histiocytic and lymphocytic infiltration. (C) Acid phosphatase reaction to highlight histiocytic infiltration. (D) CD4+ staining highlighting CD4 T-lymphocytes.

horses of all breeds but Morgans and ponies appear to be at greater risk [57]. The disease is the most common endocrinopathy in late middle-aged and geriatric horses [57]. However, horses as young as 7 years of age have been diagnosed with the disease. The disease is a primary dopaminergic neurodegenerative hypothalamic disease that results in loss of dopaminergic inhibition of the pituitary pars intermedia leading to increased melanotroph function and subsequent excessive production of proopiomelanocortin derived peptides which include α-melanocyte stimulating hormone (α-MSH), β-endorphin (β-END), corticotrophin-like intermediate lobe peptide (CLIP), and adrenocorticotropin (ACTH) [58]. Diseased horses develop hypertrophy, hyperplasia or functional adenomas of the pituitary pars intermedia.

Common clinical signs include hirsutism, considered the hallmark of the disease, hyperhidrosis, polydipsia, polyuria, muscle wasting, laminitis, and chronic or recurrent infections [57]. Muscle wasting has been reported to vary from 35% to 88% of the cases; along with abnormal fat distribution reported to be 9–67% of cases (Fig. 6A) [57]. Lethargy, weakness, poor performance and/or decreased physical activity are commonly observed features and associated with decreased muscle mass and strength [4].

Laboratory work may be normal or may include a non-inflammatory leukogram, hyperglycemia and occasional elevations of liver enzymes. Serum muscle enzyme activities are within reference values [4]. There are no specific electromyographic abnormalities [4]. Horses with PPID develop mild non-inflammatory myopathic alterations with the most prominent feature being atrophy of type 2A and 2B myofibers (Fig. 6B) [4]. Atrophic type 2 fibers have a decreased cross-sectional area, and may appear anguloid to angular in shape [4]. In addition, there is loss of type 2B myofibers, increased type 1 to type 2 myofiber ratio compared to age-matched control horses, and increased coefficient of variability indicating abnormal myofiber size variation. Lipid accumulation is observed at both inter- and intramyofiber spaces [4]. Subsarcolemmal accumulation of swollen mitochondria is observed at the ultrastructural level [4].

4. Exertional myopathies with rhabdomyolysis

4.1. Recurrent exertional rhabdomyolysis

Recurrent exertional rhabdomyolysis (RER) is the most prevalent muscle disease in Thoroughbred horses. It has been estimated that 5–10% of racing Thoroughbreds develop exertional rhabdomyolysis during a racing season with recurrences of up to 17% [59,60]. This disorder has an autosomal-dominant mode of inheritance with variable expression [9]. RER is believed to be caused by an abnormality in intracellular calcium regulation, and not by lactic acidosis [61–63]. However, important genes involved in the regulation of myoplasmic calcium such as ryanodine receptor 1 (*RyR1*), sarcoplasmic reticulum calcium ATPase (*ATP2A1*), and dihydropyridine receptor-voltage sensor (*CACNA1S*) genes were excluded from linkage to RER [64]. The disease has also been observed in Standardbreds [65].

Clinical signs include muscle cramping, sttiffness, shifting lameness, sweating, reluctance to move, tachypnea, and colic-like signs. Episodes are observed more frequently after horses reach a level of fitness then are restrained to a slower pace [59,60]. Episodes after racing occur infrequently. Exertional rhabdomyolysis has also been observed in Thoroughbreds performing other physical activities such as polo, steeplechase, and the cross-country phase of a 3-day event. Risk factors associated with RER include a young age, female, high strung, having rested for more than 1 day prior to exercise, gallop during exercise, diets consisting of more than 4.5 kg of grain per day, and concurrent lameness [59].

A presumptive diagnosis of RER can be established by clinical signs, risk factors, an increased serum CK activity 4–6 h postexercise, and myopathic features in muscle biopsy specimens. These features include centrally located nuclei in mature type 2A and type 2B muscle fibers, increased subsarcolemmal glycogen, and variable amounts of necrosis and regeneration [1,66]. In addition, RER affected horses have an abnormal in vitro contracture response to potassium, caffeine and/or halothane

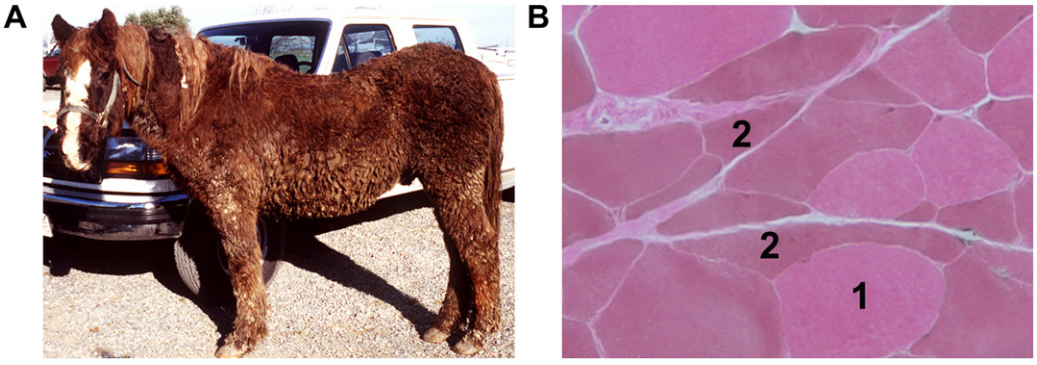

Fig. 6. Pituitary pars intermedia dysfunction. (A) Horse with PPID myopathy; note horse with hirsutism, muscle wasting, and pendulous abdomen. (B) Myofibrillar ATPase activity at pH 9.8 (25×) showing type 2 atrophy in gluteus medius muscle. Myofiber types are indicated with Arabic numbers.

[61,62,66]. Treatment consists of supportive care, anxiety and muscle pain relief, replacement of fluid and electrolyte losses, rest while recovering from rhabdomyolysis, and environmental and dietary modifications [67,68].

5. Exertional myopathies without rhabdomyolysis

5.1. Mitochondrial myopathy

Mitochondrial respiratory chain abnormalities are an important cause of neuromuscular disease in humans, and may be due to defects of the mitochondrial or nuclear genome [69]. A 3-year-old Arabian mare with normal muscle mass, stiffness and exhaustion upon only a few minutes of light exercise was diagnosed with mitochondrial myopathy caused by a deficiency of Complex I in the respiratory chain [10]. Upon exercise tolerance testing, the mare developed shifting lameness, short stride, myalgia, profuse sweating, and came to a standstill [10]. Blood gases were within reference ranges; however a marked lactic acidosis and increased hematocrit developed. Serum CK and AST activities were within reference values. On histochemical analysis, type 2A and 2B fibers stained intensively with NADH-TR and Gomori trichrome [10]. In addition, few fibers had a "ragged red" appearance. Extensive accumulation of enlarged mitochondria underneath the sarcolemma and between myofibrils was evident on electron microscopy [10]. The cristae were distorted and arranged concentrically. Lipid droplets were also prominent in the muscle fibers [10].

6. Altered muscle membrane conduction

6.1. Hyperkalemic periodic paralysis

Hyperkalemic periodic paralysis (HYPP) is an autosomal-dominant trait that affects Quarter Horses, Paints, Appaloosas, and Quarter Horse-crossbred horses [70]. The disease was first recognized in the 1980s and resembled hyperkalemic periodic paralysis in humans [71]. The disease is caused by missense mutations of the skeletal muscle sodium channel gene (*SCN4A*). All mutations in humans are on the α-subunit (Fig. 7A).

The disease in horses is linked to a popular and prolific stallion with offspring that dominate the halter-horse industry [2,72]. These horses usually have a heavy muscle build (Fig. 7B and C). It is estimated that 4% of the Quarter Horse population may be affected [72]. The disorder is caused by a missense point mutation (cytosine to guanine) of a highly conserved portion of the α-subunit of the *SCN4A* gene [2]. This mutation results in phenylalanine to leucine (F1419L) substitution (Fig. 7A) [2]. The mutation results in increased resting membrane potential, failure of a subpopulation of sodium channels to inactivate following depolarization, and excessive inward flux of sodium and outward flux of potassium resulting in persistent depolarization of muscle cells [73]. Muscle hyperexcitability results in muscle tremors, fasciculations, and weakness that can progress to paralysis when muscle cells become persistently depolarized [73].

Clinical signs may vary from asymptomatic to daily muscle fasciculations and weakness. Episodes may begin with a brief period of myotonia, prolapse of third eyelid, sweating, and focal muscle fasciculations commonly in flanks, neck and shoulders [70,74]. Muscle fasciculations may become generalized and exacerbated by attempts to move. Muscle cramps may also develop. A common feature of HYPP is weakness that may manifest as swaying, staggering, dog-sitting, and may progress to recumbency [74]. Respiratory stridor and distress, dysphagia, pharyngeal collapse, and laryngeal paralysis may also occur [75]. Deaths from severe episodes have also been reported. Horses appear normal in between episodes. Occurrence of episodes is unpredictable but some precipitating factors include sudden dietary

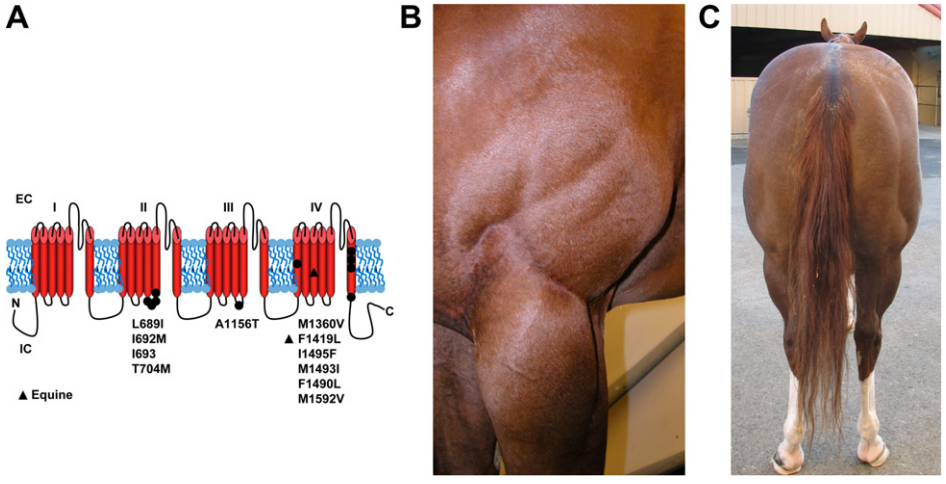

Fig. 7. Hyperkalemic periodic paralysis. (A) Diagram of skeletal muscle sodium voltage-gated channel. Diagram depicting four transmembrane domains in roman numbers, each consisting of six segments. Amino acid substitutions in humans are indicated in letters and numbers under appropriate domain. The mutations are indicated in circles for humans and triangle for the horse mutation. EC, extracellular space; IC, intracellular space; N, N-terminus; and C, C-terminus. (B and C) Horses with HYPP; note the pronounced musculature.

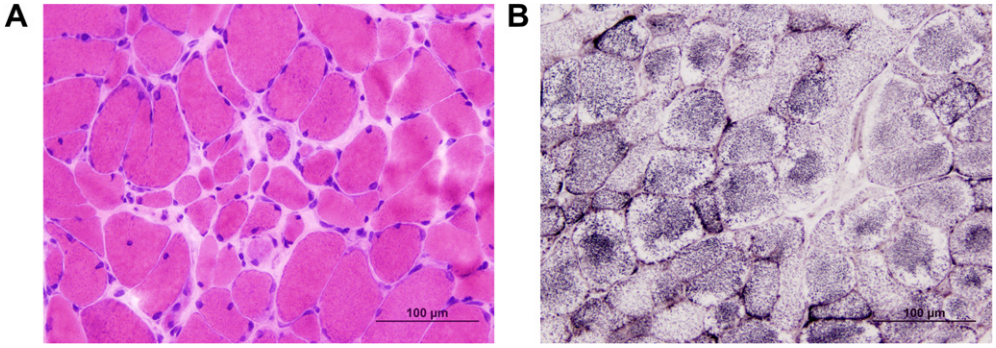

Fig. 8. Myotonic dystrophy. (A) Fresh-frozen H&E stain at 20× showing internalized nuclei, myofiber size variation, increased connective tissue, split fiber intermixed with atrophic and hypertrophic fibers, degeneration, and necrosis. (B) Fresh-frozen SDH stain at 20× showing numerous moth-eaten fibers.

changes, fasting, anesthesia, sedation, stress, transportation, rest after exercise, exposure to cold, pregnancy, and concurrent diseases [70,76,77]. Diets high in potassium (>1.1%) such as alfalfa, soybean, molasses, electrolyte supplements, and kelp-based supplements commonly trigger episodes [78].

Laboratory findings during an episode include hyperkalemia (6–9 mmol/L; reference 3–5.6 mmol/L), mild hyponatremia, and hemoconcentration [74]. Serum CK is within reference values or may be mildly elevated a few hours post-episode. Complex repetitive and myotonic discharges are observed in horses even in the absence of clinical manifestations [70,74]. Typically, there are no specific histopathological findings in skeletal muscle but mild myodegeneration and vacuoles may occasionally be observed [75]. The definitive diagnosis is through genetic testing.

6.2. Myotonic dystrophy

A severe and progressive neuromuscular disorder that resembles myotonic dystrophy in humans has been reported in Quarter Horses, Thoroughbred, and Anglo-Arab-Sardinian foals [79–82]. Predominant clinical signs include generalized and percussion myotonia, stiff or impaired gait, weakness, and testicular hypoplasia [80]. Hypertrophy, hypertonicity, and stiffness of proximal and paraspinal muscles is followed by weakness and atrophy [80]. A classic electromyographic feature is the presence of myotonic discharges (“dive bomber” sound). Histopathological findings include internalized nuclei, myofiber size variation, sarcoplasmic masses, ringbinden fibers, moth-eaten fibers, increased endomysial connective tissue, fat infiltration, split fibers intermixed with hypertrophic fibers, type grouping and clusters of angular type 2 fibers, degeneration and necrosis [80,81] (Fig. 8). Ultrastructurally, there is loss or disruption of Z bands, sarcolemmal loss with glycogen accumulation and dilation of the sarcotubular system [81]. Sensory and motor conduction velocities were investigated in a single case and found to be normal [81]. There are two types of myotonic dystrophy in humans, type 1 (DM1) and type 2 (DM2) [83]. DM1 is caused by a CTG triplet repeat in the untranslated region of the *DMPK* protein kinase gene [84]. The second type was initially referred to as proximal myotonic myopathy (PROMM) and is caused by an unstable CCTG tetrarepeat expansion in intron 1 of the zinc finger protein 9 (*ZNF9*) gene [85]. The genetic basis for myotonic dystrophy in horses has not yet been established.

7. Conclusion

In conclusion, many muscle disorders affect the horse. Some of these disorders are similar to those of man and other species, while others appear to be unique to this species. Through the continuous efforts of veterinarians, researchers, and experts in the field of muscle diseases; our understanding of myopathies regardless of the species will continue to increase. There is still much work to be done in this field. Historically, horses have been essential to humans, going side-by-side during times of war, in agriculture, for ranch work, and in transportation, entertainment, sports and leisure time. Further, horses can be companions, and more recently, have been used as a therapeutic aid for people with disabilities. Therefore, improving the health of our equine companions should be a step forward in the improvement of human health.

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