SYSTEMIC PATHOLOGY

Pathology of Muscle

Lecture 2

Paul Hanna

Winter 2017
• there are a wide variety of congenital and/or hereditary muscle conditions in animals

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene affected</th>
<th>Type of disease</th>
<th>Species/breed affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphofructokinase (PFK) deficiency</td>
<td>PFK, muscle isozyme</td>
<td>Carbohydrate metabolic defect</td>
<td>English Springer Spaniels, American Cocker Spaniels</td>
</tr>
<tr>
<td>Myophosphorylase deficiency</td>
<td>Myophosphorylase</td>
<td>Carbohydrate metabolic defect</td>
<td>Charolais cattle</td>
</tr>
<tr>
<td>Polysaccharide storage myopathy</td>
<td>Glycogen synthase 1 (GY51)</td>
<td>Carbohydrate metabolic defect</td>
<td>Horses—especially draft and Quarter Horse-related breeds</td>
</tr>
<tr>
<td>Glycogen branching enzyme defect</td>
<td>Glycogen branching enzyme (GBE1)</td>
<td>Carbohydrate metabolic defect</td>
<td>Quarter Horses, Norwegian Forest Cats</td>
</tr>
<tr>
<td>Centronuclear myopathy</td>
<td>PTPLA</td>
<td>Centronuclear myopathy</td>
<td>Labrador Retriever</td>
</tr>
<tr>
<td>X-linked myotubular myopathy</td>
<td>Myotubulin MTM1</td>
<td>Centronuclear myopathy</td>
<td>Labrador Retriever</td>
</tr>
<tr>
<td>Hyperkalemic periodic paralysis (HYPP)</td>
<td>Skeletal muscle sodium channel</td>
<td>Channelopathy leading to myotonia and paralysis</td>
<td>Impressive line of Quarter Horses</td>
</tr>
<tr>
<td>Canine myotonia</td>
<td>Skeletal muscle chloride channel—CIC-1</td>
<td>Channelopathy leading to myotonia</td>
<td>Miniature Schnauzer</td>
</tr>
<tr>
<td>Exercise-induced collapse</td>
<td>Dynamin 1</td>
<td>Episodic collapse associated with exercise</td>
<td>Labrador Retriever</td>
</tr>
<tr>
<td>X-linked muscular dystrophy</td>
<td>Dystrophin</td>
<td>Muscular dystrophy</td>
<td>Various dog breeds, DSH cats</td>
</tr>
<tr>
<td>Double muscling</td>
<td>Myostatin</td>
<td>Muscular hyperplasia</td>
<td>Various beef breeds, Whippets</td>
</tr>
<tr>
<td>Callipyge phenotype</td>
<td>CLPG1</td>
<td>Muscular hyperplasia</td>
<td>Sheep</td>
</tr>
<tr>
<td>Porcine stress syndrome</td>
<td>Ryanodine receptor</td>
<td>Malignant hyperthermia</td>
<td>Various pig breeds</td>
</tr>
<tr>
<td>Malignant hyperthermia</td>
<td>Ryanodine receptor 1</td>
<td>Malignant hyperthermia</td>
<td>Quarter Horses, dogs</td>
</tr>
</tbody>
</table>
CONGENITAL AND INHERITED MUSCLE DEFECTS

**Arthrogryposis** (= congenital articular rigidity)

- relatively common in aborted fetuses / stillborns

- can be caused by myogenic or neurogenic disorders

- often due to lack of innervation during gestation causing muscular **hypoplasia**

- neurologic defects are usually related to failure of neural tube closure (dysraphism), +/- spina bifida.

- also seen with other cord defects (eg syringomyelia, hydromyelia)

- CNS defects can be genetic OR associated with in utero exposure to toxins (eg wild lupine) or in utero viral infections (eg bluetongue and border disease)
The musculature of the limbs is poorly developed; with all muscles shortened many joints are fixed / rigid and the limbs in various combinations of flexion and extension. Also note the yellow color of the wool which is due to meconium staining and is consistent with fetal anoxia due to dystocia (ie the fixed limbs often lead to difficult / prolonged deliveries.)
Arthrogryposis

Fig 3-38 Newborn calf with arthrogryposis.  

Animals affected with arthrogryposis often have spinal cord defects (myelodysplasia)

Fig a - note the cleft (dysraphism / myeloschisis) in the spinal cord (arrows)
Fig b - note the abnormal cavitations (syringomyelia) in the cord (arrowheads)
CONGENITAL AND INHERITED MUSCLE DEFECTS

Metabolic Myopathies

- abnormal skeletal muscle metabolism can lead to muscular dysfunction
- mostly due to mitochondrial dysfunction or altered glycogen or fatty acid metabolism
- a variety of these syndromes have been described in dogs, cats, cattle & horses
Equine Polysaccharide Storage Myopathy (PSSM)

- a glycogen storage myopathy seen in many horse breeds
- AD with variable expression; defects in CHO metabolism (eg GYS1)
- asymptomatic to progressive weakness / lameness / muscle atrophy to exertional rhabdomyolysis
- histo: accumulation of polysaccharides and degeneration / necrosis in type 2 fibers

Fig 3-66 (Maxie) A. Normal glycogen staining pattern of horse muscle. B. Multiple myofibers with peripheral aggregates of densely stained glycogen in an Arabian horse with polysaccharide storage myopathy.

Fig 15-35 (Zachary) Equine PSSM. C. Severe form, showing PAS positive inclusions which are not digested by amylase and are characteristic of complex polysaccharide
Malignant Hyperthermia

- rare in dogs, horses & humans
- common in pigs → Porcine Stress Syndrome (PSS) & Pale Soft Exudative Pork (PSE)
- triggered by drugs (eg halothane) and in pigs fighting / exercise / heat / etc
- clinically see severe muscle rigidity, hyperthermia, respiratory & metabolic acidosis, myoglobinemia, hyperkalemia, cardiovascular collapse and death
Malignant Hyperthermia

• pathogenesis: mutated RyR (AR trait) → unregulated Ca\(^{2+}\) release → ↑ myofiber contraction → ↑ body temperature → continued contraction causes myofiber degeneration / necrosis → protein denaturation / leak into ECF → ↑ interstitial edema

Pigs with malignant hyperthermia have a mutation in RYR. Certain triggers (eg fighting, heat, halothane) can alter RyR leading to unregulated calcium release from the sarcoplasmic reticulum causing severe prolonged myofiber hypercontraction progressing rapidly to degeneration / necrosis.
Gross pathology:

- muscles with higher proportions of type 2 fibers (back / hindlimbs) are pale and wet
- also severe pulmonary edema and hydropericardium / hydrothorax / ascites

Markedly pale muscles with abundant edema in fascia and exuding from cut surfaces

Marked pallor of the epaxial (eg longissimus) muscles
Pale soft exudative (PSE) pork

Varying degrees of pallor in cuts of pork; also have soft (putty-like) texture and accumulation of fluid in packing tray (lower right)

http://www.fao.org/DOCREP/003/X6909E/x6909e04.htm
Malignant Hyperthermia

- Histopathology: acute myofiber degeneration / necrosis & interstitial edema

Fragmented fibers (asterisk) and retraction cap/cup (arrow) indicative of acute myofiber degeneration / necrosis
Splayleg in piglets

Splay Leg Tape
- self-adhesive, anti-splay tape to counteract splay leg

www.youtube.com/watch?v=H4lEEYf2q14

www.kerbl.com
"Double muscling" (muscular hyperplasia)

Fig 3-43 (Maxie) Whippet dog with muscular hypertrophy ("bully whippet") caused by defective myostatin.

"Double muscled" Belgian blue bull. Congenital muscular hyperplasia ("double muscling") in a bull caused by defective myostatin.
CONGENITAL AND INHERITED MUSCLE DEFECTS

Muscular steatosis

Bovine, skeletal muscle, muscular steatosis (fatty infiltration). Replacement of muscle tissue with mature adipose tissue.

Bovine, skeletal muscle with prominent fatty infiltration (also called “steatosis”). Usually subclinical and typically a problem only in meat inspection.
Muscular Dystrophy

Fig 27-10 (Robbin's) Relationship between the cell membrane (sarcolemma) and the sarcolemmal associated proteins. Dystrophin, an intracellular protein, forms an interface between the cytoskeletal proteins and a group of transmembrane proteins, the dystroglycans and the sarcoglycans. These transmembrane proteins have interactions with the extracellular matrix, including the laminin proteins. Dystrophin also interacts with dystrobrevin and the syntrophins, which form a link with neuronal type nitric oxide synthetase (nNOS) and caveolin. Mutations in dystrophin are associated with the X-linked muscular dystrophies; mutations in caveolin and the sarcoglycan proteins with the limb-girdle muscular dystrophies, which can be autosomal dominant or recessive disorders; and mutations in the α2-laminin (merosin) with autosomal recessive congenital muscular dystrophy.
**Myotonic and Spastic syndromes**

- *myotonia* is defined clinically as a temporary inability of skeletal muscle to relax

- most myotonias result from muscle membrane electrical abnormalities, esp ion channel defects for regulation of sodium or chloride (also called “channelopathies”)

The normal action potential in the muscle membrane (illustrated in the above diagram) primarily involves sodium and potassium fluctuations. So defects in the sodium channel can alter the resting muscle membrane potential which can lead to increased muscle action potentials (with muscle fasciculations and spasms) &/or complete depolarization (hypotonia / collapse). Chloride channel mutations can also affect membrane excitability (eg exaggerated response to stimulation).
Hyperkalemic periodic paralysis (HYPP) of horses

- underlying defect in the muscle sodium channel → increased open time (DNA test available)

- see increased influx of sodium; results in compensatory potassium efflux (hence hyperkalemia)

- see initial mild signs of hypertonia followed by transient paralysis / collapse (hypotonia)

Fig. 42-4 Myotonic dimpling of the triceps in a horse with hyperkalemic periodic paralysis.

Fig 42-6 A horse suffering from an episode of HYPP.
spastic syndromes are also associated with tightening of the muscles, causing stiff and awkward movement

Scottie Cramp is an AR trait. Following excitement or exercise see a progressive increase in muscle tone causing lumbar kyphosis and decreased flexion of the pelvic limbs; +/- falling over. A deficiency of serotonin activity in the spinal cord gray matter has been implicated as the underlying cause

Fig 12-42 A Holstein calf with spastic paresis. Notice that although the calf is standing still she keeps the left pelvic limb extended caudally. Rebhun's Diseases of Dairy Cattle, 2nd Ed
Neuromuscular endplate with locations of pre-synaptic, synaptic and postsynaptic proteins involved in congenital myasthenic syndromes

Green line represents synaptic basal lamina. Red line represents acetylcholine receptor on crests of the junctional folds. Blue line represents LRP4, MuSK, Dok-7, and rapsyn closely associated with the acetylcholine receptor.

Downer syndrome

- in large animals following prolonged recumbency (disease / anesthesia) → the weight of the body compresses the muscles → inadequate vascular perfusion pressure (+/- thrombosis)

- ~ 6-12 hours get ischemic necrosis of pectoral or limb muscles that are tucked under the body

- muscle necrosis from Downer syndrome then becomes a reason the animal can’t rise
Downer syndrome

Serial transverse sections of a leg from a cow with a history of being down for several weeks. Dark areas of necrosis and hemorrhage (asterisks) involving several muscle groups. Necrosis is due to physical trauma, compressive ischemia and thrombosis (see next slide for close-up).
Downer syndrome

Image to the left shows close up of areas of muscle necrosis with hemorrhage in the leg (asterisks)

Close examination of the affected leg (image to the right) reveals a large thrombus in a major vessel (arrows)
Compartment syndrome

- characterized by degeneration / necrosis in muscles surrounded by heavy aponeurosis

- pathogenesis: muscular swelling / expansion associated with injury in a non-expandable compartment → results in vascular compression → ischemia and infarction of the muscle

Fasciotomy of the lower limb in a human to treat compartment syndrome.
Compartment syndrome

Deep pectoral myopathy

- frequently seen in poultry, esp heavily muscled breeds of turkeys & chickens
- disease is preceded by a brief but vigorous period of wing flapping → few hrs later localized area of degeneration and necrosis in the deep breast (supracoracoid) muscle

Greenish color of the supracoracoid pectoral muscle due to degeneration and necrosis (arrow). Photo to right is close up.
Ischemic necrosis supracoracoid muscle (cooked specimen): Dark appearance of necrotic muscle found in this cooked chicken (asterix). Lesions appear a few hours after exercise and because they are deeply “buried in the pectoral muscles they are sometimes not grossly detected until "supper time."
Postanesthetic myopathy in horses

- seen in 3-6% horses undergoing prolonged recumbency
- pathogenesis: compressive pressure due to large weight of animal during recumbence &/or muscle hypoxia from systemic hypotension associated with the general anesthetic
- ranges from muscle swelling with lameness to paresis with renal failure / shock

Fig 11-11 A horse with postanesthetic myopathy of the right gluteal muscles. The severe swelling is notable. The horse recovered fully with supportive care.
NUTRITIONAL MYOPATHY (WHITE MUSCLE DISEASE)

• in older vet literature was mistakenly called nutritional muscular dystrophy

• associated with dietary deficiency of Sel &/or Vit E

• other factors → exercise, environment, other nutrition factors / toxicants

• relatively common; esp young, rapidly growing, well-conditioned sheep, cattle, pigs

• in pigs it may be independent or coexist with other Sel / Vit E deficiency diseases

• less common in foals & goats & other species.
NUTRITIONAL MYOPATHY (WMD)

- pathogenesis: inadequate amounts of radical-scavenging Sel / Vit E → lipid peroxidation of membranes → influx of Ca\(^{2+}\) into sarcoplasm → hypercontraction & activation of proteases → myofiber degeneration / necrosis and often calcification

- with cell membrane damage intracellular enzymes (eg CK) leak into ECF / serum

- muscles with many type 1 fibers more severely affected (diaphragm, intercostals, tongue)
Nutritional myopathy (WMD)

Gross Pathology:

- muscle pallor; can be subtle in mild cases or inapparent in peracute cases
- in severe cases, muscles are pale with chalky white areas or streaks

Close-up of affected skeletal muscle in a calf show prominent pale streaking.
WMD lamb
Pallor and white streaking in skeletal muscle of a lamb with white muscle disease. The extensive calcification of degenerate/necrotic myofibers that often occurs with WMD accounts for this pronounced white discoloration (as compared to the more subtle pallor seen with myodegeneration without calcification)
NUTRITIONAL MYOPATHY (WMD)

WMD Foal. Extremely pale muscle (W) from a few days old foal that died of WMD. Note the normal color of equine muscle (N).

WMD Pig
The musculature of this pig with WMD was slightly pale. However, because normal porcine muscle is often pale, histopathology was required to confirm the muscle degeneration / necrosis in this case. Pigs can develop other diseases with Vit E / Sel deficiency (eg mulberry heart disease & hepatosis dietetica) which can occur independently or together.
Remember to inspect the heart. Calf heart (right) showing patchy areas of chalky white discoloration in the left ventricular myocardium.
Fragmented myofibers with swelling, hyalinization and loss of striations in some areas (asterisks) and extensive blue-purple granularity, representing calcification (arrows), in other areas. H&E

Special staining is often used to confirm calcification. In this figure the calcified myofibers stain dark with Von Kossa stain.