ACQUIRED MYASTHENIA GRAVIS:
BEYOND BAILEY CHAIRS

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Veterinary Neurology of the Chesapeake
Outline

- Case Presentation
- The Neuromuscular Junction
- Acquired Myasthenia Gravis
  - Pathophysiology
  - Clinical Presentation
  - Diagnosis
  - Treatment
  - Prognosis
  - Future Directions
Case Presentation
Sage

- 7 YO SF DLH
- Acquired as a kitten
- Indoors only
- Up to date on vaccines
- Previously healthy
- No medications
- **Owned by a veterinarian**
Sage: Differentials

- Oral cavity disease
  - Resorptive lesions
  - Fractured teeth
  - Mass – abscess vs neoplasia
  - Foreign body

- Pharyngeal Disease
  - Mass – polyp vs abscess vs neoplasia
  - Cricopharyngeal achalasia
  - Foreign body

- Esophageal Disease
  - Megaesophagus
  - Foreign body
  - Mass

- Neuromuscular diseases
Sage: Examination

- **Physical Examination:**
  - Normal sedated oral examination
  - Matted fur, but otherwise normal examination

- **Neurological Examination:**
  - Ambulatory without signs of paresis or ataxia
  - Normal cranial nerves – no gag performed
Sage: Diagnostics

- CBC, Chemistry, T4, Urinalysis: Normal

- Thoracic radiographs:
  - Gas dilation of the esophagus

- Abdominal ultrasound:
  - Mild mesenteric lymphadenopathy
    - Histopathology: reactive lymph nodes
Sage: Diagnostics

- Acetylcholine receptor antibody test:
  - 10.9 nmol/L (reference <0.3 nmol/L)

- Diagnosis: Acquired, focal myasthenia gravis
The Neuromuscular Junction (NMJ)
NMJ: Anatomy

- Skeletal muscle fibers are innervated by large, myelinated nerve fibers
  - Each nerve fiber branches and stimulates from three to several hundred skeletal muscle fibers

- Each nerve ending makes a junction
  - *Neuromuscular junction*

NMJ: Anatomy

Diagram Credit: http://bioserv.fiu.edu/~walterm/Fund_Sp2004/review_fall05_bone_musc.htm
NMJ: Acetylcholine Production

- Acetylcholine (ACh) is synthesized in the cytoplasm of the nerve terminal
  - Absorbed into synaptic vesicles → quanta
  - Quanta: 1000-5000 molecules of Ach

Diagram Credit: Physiology of Domestic Animals, Figure 3.8
NMJ: Acetylcholine Secretion

- Neuronal action potential triggers calcium influx
  - Calcium influx triggers exocytosis of vesicles into the synaptic cleft

Diagram Credit: http://pharmacology-online.blogspot.com/2011/04/cholinergic-transmission.html
NMJ: Acetylcholine Receptors (AChR)

- Ligand-gated ion channels
  - Located in subneural clefts
  - Nicotinic AChR

- Activation triggers Na+ influx $\rightarrow$ Miniature Endplate Potential (MEPP) $\rightarrow$ Muscular Contraction

Diagram Credit: http://www.nature.com/nrn/journal/v11/n6/fig_tab/nrn2849_F1.html
NMJ: Acetylcholinesterases

- Acetylcholinesterase (AChE) is concentrated within the synaptic cleft
  - $\text{ACh} \rightarrow \text{acetate} + \text{choline}$

- Diffusion of ACh out of the synaptic cleft

Diagram Credit: Neuroscience, 4th Edition
NMJ: “Safety Factor”

- The ratio between the number of ACh quanta released and the number of ACh quanta required for depolarization of a muscle fiber
  - How much interference can be tolerated before there is failure of neuromuscular transmission

- Typically, ACh quanta released >>>> ACh quanta required
Myasthenia Gravis (MG)

“Severe muscular weakness”
MG: Pathophysiology

- Disorder of neuromuscular transmission
  - Deficiency or functional disorder of nicotinic AChR within the NMJ $\rightarrow$ loss of the “safety factor”
  - Congenital and acquired forms

- MG is the most well studied and well characterized neuromuscular disease
Acquired MG: Pathophysiology

- Antibody mediated autoimmune disease\(^1\)
  1. Antibodies are present at the NMJ
  2. Anti-AChR antibodies cause clinical signs of MG when injected into rodents
  3. Immunization of animals with AChR reproduces MG
  4. Therapies that remove antibodies decrease the severity of MG clinical signs

1: Conti-Fine et al., 2006.; Journal of Clinical Investigation
A Complement binding and activation at the NMJ

B Antigenic modulation

C Functional AChR block

Conti-Fine et al., 2006.; Journal of Clinical Investigation
Acquired MG: Dogs

- Bimodal age distribution
  - Modes of distribution at 3 years and 10 years of age
  - Higher relative risk: Akitas, terrier group, Scottish terriers, and German shorthaired pointers
  - Inherited predisposition: great Danes and Newfoundlands
  - No sex predilection

1: Shelton et al., 1997; JAVMA. 2: Ducote et al., 1999; Compend Cont Educ Practi Vet. 3: Kent et al., 2008; JSAP. 4: Lipsitz et al., 1999; JAVMA.
Acquired MG: Cats and beyond

- Abyssinian cats may have a higher relative risk than other purebred cats\(^1\)

- Acquired MG has been reported in:
  - 10 year old captive male Siberian tiger\(^2\)
  - 7 month old neutered male ferret\(^3\)
  - 7 month old Hereford heifer\(^4\)
    - “Myasthenia gravis-like syndrome”

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Acquired MG: Examination

- **Focal MG:**
  - 36-43% of canine patients\(^1\)
    - Weakness present in one or more muscle groups
    - May see facial weakness or megaesophagus
    - Typically no clinical evidence of thoracic or pelvic limb weakness
  
  - 14.3% of feline patients\(^2\)
    - Focal MG associated with megaesophagus and dysphagia

1: Khorzad et al., 2011; JVECC. 2: Shelton et al., 2000; JAVMA
Acquired MG: Examination

- **Generalized MG:**
  - 57-64% of canine patients\(^1\)
    - Mild to severe weakness, often episodic
    - Pelvic limbs affected more than thoracic limbs
    - Megaesophagus and regurgitation may be present

- 74% of feline patients\(^2\)
  - Generalized weakness
  - Megaesophagus and/or dysphagia: 20%
  - Generalized weakness associated with hyperthyroidism and methimazole: 4.8%

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1: Khorzad et al., 2011; JVECC. 2: Shelton et al., 2000; JAVMA
Acquired MG: Examination

- **Fulminant MG:**
  - < 5% of canine patients \(^1\)
    - Acute onset and rapid development of clinical signs
    - Non-ambulatory tetraparesis to tetraplegia
    - Respiratory distress +/- aspiration pneumonia

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\(^1\) Khorzad et al., 2011; JVECC.
Acquired MG: Differentials

- Myasthenia gravis
- Polymyositis
- Idiopathic polyradiculoneuritis
- Botulism toxicity
- Tick paralysis
- Metabolic: hypoglycemia, hypocalcemia, hypokalemia, hyperkalemia
- Endocrine: hypoadrenocorticism, hypothyroidism
- Toxicity: organophosphates, carbamates
- Orthopedic disease
Acquired MG: Diagnostics

- CBC, Chemistry, Urinalysis, T4, +/- ACTH stimulation
  - R/O metabolic and endocrine causes of weakness

- Chest radiographs +/- CT
  - Megaesophagus
  - Aspiration pneumonia
  - Thymoma
    - 5% of dogs with MG have a thymoma
    - 25% of cats with MG have a thymoma
  - Metastatic disease
    - MG may occur with cholangiocellular carcinoma, CNS lymphoma, and anal sac adenocarcinoma

Acquired MG: Diagnostics

Thymoma

Megaesophagus

Photo Credit: http://www.vetmed.ucdavis.edu/vsr/Neurology/Disorders/Myasthenia%20Gravis.html
Acquired MG: Diagnostics

- Radioimmunoassay for AChR-antibody titers
  - Gold standard for diagnosis of acquired MG
    - Sensitive (98%) and specific (100%)
  - False negative results (~ 2%)
    - Loss of critical determinants on the AChR during sample preparation
    - Low titers of high affinity antibodies
    - Antigenic differences in AChRs
    - Antibodies directed against endplate determinants other than AChRs
    - Prior glucocorticoid administration
  - Cons: Time!

1: Shelton G.D., 1998; ACVIM Forum. 2: Shelton et al., 1990; JVIM.
Acquired MG: Diagnostics

- **Tensilon Test**
  - Edrophonium chloride
    - Short-acting anticholinesterase
  - **Side effects:**
    - Salivation, retching, vomiting, diarrhea
    - Pre-treatment with atropine
      - Be prepared to intubate
  - **Cons:** False positives and false negatives
Acquired MG: Diagnostics

- **Electrodiagnostics**
  - **Repetitive Nerve Stimulation**
    - Recording of compound-muscle action potentials after electrical stimulus is applied to the ulnar or tibial nerve.
    - Looking at the summation of action potentials from several nerve fibers and from a number of motor units.
  - **Single-fiber electromyography**
    - Selective recording of action potentials from 2-3 muscle fibers innervated by a single motor unit.
    - Evaluation of the NMJ “safety margin”
    - The most sensitive test for the diagnosis of MG in humans (92-100%)
  - **Cons**: Require general anesthesia

Acquired MG: Treatment

- Anticholinesterase Therapy
  - Pyridostigmine bromide (Mestinon) or neostigmine bromide (Prostigmin)
    - Prolong the action of ACh at NMJ via competitive inhibition of AChE
  - Adverse effects: diarrhea, abdominal pain, hypersalivation, weakness, lacrimation, bradycardia, cholinergic crisis

1: Foy et al., 2011; JVECC.
Acquired MG: Treatment

- Immunomodulatory therapy
  - Corticosteroids
  - Azathioprine
  - Cyclosporine A
  - Mycophenolate mofetil

- Immunosuppression has been the only mode of treatment shown to significantly decrease patient mortality\(^1\)
  - Even in the presence of aspiration pneumonia

1: Dewey et al., 1997; JVIM.
Acquired MG: Treatment

- **Nutritional Management**
  - Elevated Feedings
    - Bailey Chairs
    - Platforms
    - Inclines/stairs
  - Gastrostomy tubes
    - Require anesthesia
    - Reduced risk of aspiration
Acquired MG: Treatment

- Mechanical Ventilation
  - Severe aspiration pneumonia, respiratory failure

- Avoid:
  - Phenothiazines, aminoglycosides, ampicillin, anti-arrhythmics, and fluoroquinolones

- Supportive Care
  - Down dog care: urinary catheterization, flipping hips, prevention of pressure sores and urine scald

1: Foy et al., 2011; JVECC.
Acquired MG: Prognosis

- **Spontaneous remission**
  - In 47/53 (88%) dogs treated with only anticholinesterase therapy, immune remission was seen within 6.4 months (range: 1-12 months)\(^1\)

- **Overall, prognosis is guarded**
  - Generalized megaesophagus
    - Median survival time: 90 days\(^2\)
    - 19/71 (26.7%) died prior to discharge
  - Aspiration pneumonia
  - Respiratory distress
  - 1 year survival rate for 25 dogs was 40.4%\(^3\)

1: Shelton et al., 2001; Neurology 2: McBrearty et al., 2011; JAVMA. 3: Dewey et al., 1997; JVIM.
Acquired MG: Future Directions

- Evaluation of new treatment options
  - Human intravenous immunoglobulin (hIVIG)
  - Plasmapheresis
  - MG vaccines

- Controlled prospective studies evaluating immunosuppressive agents
Back to Sage…

- **Treatment:**
  - Prednisone
  - Gastrostomy tube
  - Cyclosporine

- **AChR titers:**
  - 4/2013: 7.7 nmol/L
  - 10/2013: 3.3 nmol/L
  - Relapse 11/2013
Questions?
References

- Guyton and Hall 12th Edition
References

- Wray J.D., Sparks A.H. Use of radiographic measurements in distinguishing myasthenia gravis from other causes of canine megaoesophagus. *JSAP* 2006;47:256-263.