Understanding Equine Endocrinopathic Laminitis

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Overview

- A case...
- Pathophysiology of EMSAL – what we know, and what we need to learn
- Diagnostic testing for equine ID, PPID
- Treatment of affected animals

History

- 13 year old TWH/Morgan cross gelding
- Same owner for >10 years
- Pleasure trail riding
- No history of laminitis
- ‘Injury to RF foot’ in several years ago

July

- First presentation to OSU VMC
- Presented for 6 day history of bilateral forelimb lameness (R > L)
- Owner reported that horse had visibly gained weight over last few months
- BW = 1150 lb
- BCS = 8.5/9 (prominent regional adiposity)

- Mild elevations in DP’s, both front feet
- Obel grade II/IV
- Hoof tester (+) at toe, RF (no response in other feet)
Acute laminitis ‘ER’ treatment: 
*What to do first*

- Address underlying cause, if it can be identified
- Stall restriction
- Deep bedding
- Minimize dietary NSC (sugar, starch, and fructan)
- Analgesia (NSAID – usually PBZ unless some contraindication)
  - Other options – acetaminophen, gabapentin, butorphanol, ketamine...
- Frog support/heel elevation
- Ice?
  - Likely helpful, but depends on circumstances

**Initial Management**

- Podiatry
- Medication
  - Phenylbutazone (1 g PO BID for 7 days, then 1 g PO SID for 10-14 days)
  - Levothyroxine (48 mg PO SID)
  - Metformin (15 mg/kg PO BID)
- Diet
  - Concentrate
  - Forage – recommended tested low-NSC source
- Plan for follow up
  - Pedal radiographs in 4 weeks
  - Endocrine testing

**Endocrine Testing**

*Insulin Dysregulation and PPID*
Evaluation of Equine ID

- Signalment and historical information
- Laminitis diagnostics
- **Insulin dysregulation** testing (many available tests)
  - **CAVE** comorbid disease, medications that can alter test results
    - Corticosteroids – induction of ID
    - Levothyroxine – improve SI
    - Pain (laminitis) – induction of ID

*Test conditions are important for interpretation!*
- Conservative low-NSC grass hay feeding overnight
- Pull all feed 2 hours prior to testing in the a.m.
- Should be observed, regardless of the test chosen

FSIGTT

- One of the gold standard tests (and the one that’s more amenable to field application)
  - 3 hours
  - MANY blood samples
  - MinMod kinetic analysis

FSIGTT

- Extracted indices:
  - SI, tissue insulin sensitivity index
    - mU/L x min⁻¹
  - SG, glucose effectiveness (the ability of glucose to enhance its own disappearance at basal insulin)
  - AIRg, pancreatic responsivity to glucose in 1st 10 min after injection
    - mU/L x min
  - DI, disposition index (= SI x AIRg), measure of acute beta-cell compensation for IR

Euglycemic Hyperinsulinemic Clamp

- The other gold standard test
- Infusion pumps
- 3 hours
Basal Insulin/Glucose Concentrations

- **Advantages**
  - Fast – serum sample
  - Easy
  - Inexpensive
  - Easier to repeat for monitoring

- **Disadvantages**
  - Not a dynamic test
  - Sensitivity = poor
  - False-negatives common!!

>20 mIU/L supportive of ID

1 mIU/L = ~6.9 pmol/L

Oral Sugar Test (OST)

- Frank et al ACVIM Forum 2010 (abstract)
- Dynamic test
- Used to categorize ID status for horses enrolled in multi-center EMS study...

- Designed for easy field use!
  - 1. Administer light corn syrup PO – owner can do this prior to farm call
  - Draw blood 60-90 minutes after dosing, measure [insulin]
    - [Insulin] >60 mIU/L at either time point suggests ID

15 ml/100 kg BW (~75 ml for 500 kg horse)

Insulin-Response Test (Insulin Tolerance Test)

- Bertin and Sojka-Kritchevsky (Dom Anim Endo 2013)
  - 0.1 IU/kg regular insulin IV
  - BG measured at 0 and 30 min post-injection
  - ID = <50% reduction of BG from baseline at 30 min
  - Measures tissue insulin sensitivity
1. Basal insulin/glucose
2. Oral sugar test
3. IV insulin tolerance test

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Testing for PPID

- Signalment and historical information also important!
- Laminitis diagnostics
- **Insulin dysregulation** testing (laminitis risk in PPID...)
- Evaluation of *pars intermedia* function

**Test conditions are still important for interpretation!**
- Conservative low NSC grass hay feeding overnight
- Pull all feed 2 hours prior to testing in the a.m.
- Should be standardized between assessments

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**eACTH**

- Not specific for *pars intermedia*
- Immunoreactive vs. functional ACTH
- Commercially available
- Comparisons between assays
  - Can give disparate results in same patient
  - Use same lab for initial and follow-up testing

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**eACTH**

- Seasonality
- Pulsatile secretion?
- Plastic EDTA tube
- Chilled, plasma separated within 1-2 h
- Note units!

**Effect of feeding:**
- Fed horses have higher eACTH and TRH-stimulated ACTH
- Standardization needed

- What if between 50-100 pg/mL in October?
  - Re-test in 3-6 months
  - More sensitive test...

**November-July:** <35 pg/mL
**July-November:** <100 pg/mL
TRH Stimulation Test

- TRH elicits secretion of ACTH, α-MSH in normal horses
- Does this to an even greater degree in PPID patients
- Sensitivity: ACTH > cortisol as output variable
- Seasonality

Fig. 1: AUC for adrenocorticotropic (ACTH) concentrations (•) and cortisol concentrations (□) in normal (CN) horses and the pituitary pars intermedia dysfunction (PPID) horses. The ordinate is in pg/mL. The AUC for ACTH was not statistically different between groups.

Beach et al JVIM 2011

Current recommendations:

- Autumn/early winter
  - eACTH (interpreted according to seasonally-adjusted reference ranges)
  - Avoid TRH stimulation, DST during this period
- Late winter/spring/summer
  - eACTH
  - TRH stimulation
  - (DST)
- Don’t forget to assess insulin sensitivity
- Don’t forget about the option of empiric treatment!

What about combination testing?

30% of PPID cases have ID...

TRH Stimulation Test

- Baseline blood sample
- Administration of 1 mg TRH IV
- Additional blood sample at 10 min (or 30 min)
- Measure ACTH
  - 10 min: >110 pg/mL
  - 30 min: 65 pg/mL

No seasonally-adjusted reference ranges widely accepted yet, so avoid testing in autumn/early winter
OST and TRH stimulation test

Effect of withholding feed on thyrotropin-releasing hormone stimulation test results and effects of combined testing on oral sugar test and thyrotropin-releasing hormone stimulation test results in horses

OST done FIRST...

What about TRH stimulation done first??

These were healthy horses...

ITT and TRH stimulation test

Evaluation of combined testing to simultaneously diagnose pituitary pars intermedia dysfunction and insulin dysregulation in horses

Conclusions and Clinical Importance: Combining the TRH stimulation test and the 2-step insulin sensitivity test appears to be a useful diagnostic tool for equine practitioners in the field, allowing testing of a horse for both PPIID and ID simultaneously.

Insulin signaling and laminitis

‘Endocrinopathic laminitis’ = related to hyperinsulinemia
Insulin and Laminitis

- Pleiotropic hormone
- Glucose disposal
- Mitogenesis, extracellular matrix metabolism, etc.
- Asplin et al:
  - Hyperinsulinemia precipitates laminitis

Digital lamellar insulin signaling

- Distribution of InsR is limited within digital laminae
- Distribution of IGF-1R is more extensive
- Dysadhesion from laminar basal epithelial cells from BM occurs during EMSAL, for which hyperinsulinemia is a risk factor; this suggests that:
  - 1. Effects of insulin on LBECs are indirect
  - 2. Insulin signals to LBECs directly through receptors other than InsR (eg, IGF-1R)

Lamellae do not appear to be insulin-dependent...
Glucose metabolism within keratinocytes

Glucose transport in the equine hoof

AUCg in ID
Energy regulation and laminitis

Links to epithelial structure, function

AMPK Activation

<table>
<thead>
<tr>
<th>Digital laminae</th>
<th>Liver</th>
<th>Middle gluteal m.</th>
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<tr>
<td>Lean CON</td>
<td>Lean CHO</td>
<td>Obese CHO</td>
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<td>pAMPK</td>
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<td>β-actin</td>
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mTOR

AMPK

1. Energy regulation and laminitis links to epithelial structure, function.
2. AMPK Activation.
3. Diagram showing AMPK and mTOR interactions.
Endocrinopathic Laminitis: Dietary CHO challenge

Why investigate AMPK/mTOR balance?

- Regulated under metabolic conditions affecting horses and ponies with ID
- Directly links metabolic dysregulation with epithelial cell polarity and ECM ‘connectedness’
- Therapeutic target – available agonists (many)
  - Lamellae (direct effects)
  - Rest of the horse/pony (improve ID)
- Metformin
- Exercise
- Adiponectin
- AICAR
- Aspirin
- Resveratrol

And now, back to Casey...
August - LF

Progress

- Did very well for ~2 years
- Did not lose much BW (<5% of starting weight)
- Regular work (20-30 miles of trail riding/week)
- Improvement in endocrine testing
  - Basal [insulin], [glucose] - WNL
  - OST - WNL

August - RF

August
Endocrine testing

- Basal [insulin], [glucose]
  - [Insulin] = 67 mIU/L
  - [Glucose] = 95 mg/dL
- FSIGTT
  - SI = 0.72 mIU/L/min
- OST
  - [Glucose] = 156 mg/dL at 60 min, 130 mg/dL at 90 min
  - [Insulin] = 130 mIU/L at 60 min (not measured at 90 min)
Rechecks

- Every 6-8 weeks until benchmarks are met...
- Body weight
- Body condition score
- Photographs (left, right, front, back; above, if possible)
- Bloodwork – insulin, glucose, triglycerides, leptin
- Dynamic testing – ITT, OST
- Pedal radiographs

**Benchmarks: BCS, body weight, normal endocrine testing**

Three years later...

- Presented for acute laminitis
- No change in diet
- Horse turned out on dirt lot – strict control of pasture access (currently none)
- Horse doesn’t graze during trial rides
- Hospitalized for ~10 days (owner concerns)
- ~Sound at walk by Day 4
  - Firocoxib 57 mg PO SID
  - Omeprazole (Gastrogard™) 1 mg/kg PO SID
  - eACTH on Day 10 – elevated (350 pg/mL)

**Pergolide mesylate (Prascend™): 0.5 mg PO SID for 2 weeks, then 1 mg PO SID**

Wrap-up...

- Adjusted pergolide dose
- De-rotated again (~6 months)
- Horse has labs every 6 months, dose adjustments as needed
  - Pergolide (2.5 mg PO SID)
  - Cyproheptadine (0.3 mg/kg PO BID)

**Doing well! 😊**

Thank you!

Remember to download the CE certificate in the handouts panel of the webinar control panel.

**NOTICE:** CE certificate not available for watching the recording.

Questions about CE?

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Questions about topic?

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Thank you for joining us!
Endocrinopathic Laminitis: EHC

- RelativeIntensity
  - phospho-RPS6/Actin
  - phospho-AMPK/Actin

EHC - cryotherapy

- RelativeIntensity
  - P-RPS6 (S240/244)