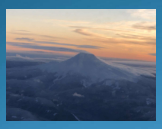
Neurologic Manifestations of Metabolic Disease



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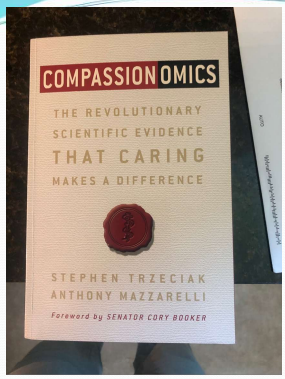
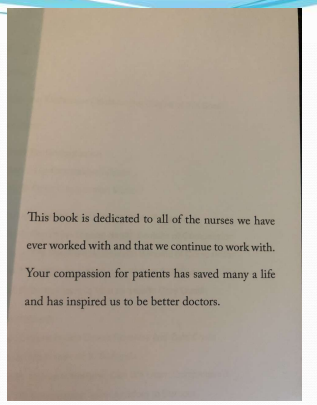
Metabolic Causes of Neurologic Dysfunction

- Such cases can present with confusing clinical signs
- Must pursue thorough physical and neurologic examinations
- Performance of appropriate diagnostics
- Importance of evaluating the entire patient
- The pitfalls of "tunnel vision"





What you see is not always what you get .....

- Interpretation of bloodwork
- Is there are trend ?
- Paying attention to the clues
- Answers can be elusive

Evaluation of the Neurologic Patient

- Does this patient have disease of the nervous system ?
- If so, it it brain, spinal cord or neuromuscular in origin ?
- Neurologic examination
  - Are the signs focal or diffuse ?
- Differential list

Case 1:

- Charlie Mettler
- 5 year old MC
- Cocker spaniel
- Presenting complaint:
- Status epilepticus

Charlie: History

- "Not right" for the last month / grumpy
- PU/PD for the last 2 weeks
- Eyes got very red after vaccinations and stayed that way
- Previous to this, very healthy / no toxin exposure

Charlie: Bloodwork / UA

- UA:
  - SG: 1.009
  - Protein: 2+
  - Active sediment

Charlie: Presenting Complaint

- Status epilepticus
- Sent from LDVM with the following bloodwork
  - Blood glucose 116, then 25 mg/dl in status
  - PCV: 82 % / TP 8.2 mg/dl

Charlie: Initial Presentation

- PCV 82 %
- Severe chemosis / hyperemia
- Blood cultures / Urine c/s
- Treatment for seizures
- Immunoreacitve insulin to assess decreased blood glucose
- Blood gas / ACTH stimulation

Charlie: Bloodwork

- CBC
  - WBC: 16,500
    - Segs 13,695
    - Bands 330
    - Lymphs 660
    - Monos 1506
  - Adequate platelets
  - Normal serum chemistry (PP=6.2/TP=4.2)

Charlie: Clinical signs

- Stuperous – treated with phenobarbital and pentobarbital to control status epilepticus
- Injected sclera / mucous membranes
- Harsh lung sounds
- Melena
- Rest of neurologic exam normal

Neurolocalization

- Forebrain
  - Status epilepticus
  - Behavior changes noted previously

Erythrocytosis

- Relative
  - Occurs when the PCV elevates with a normal RBC mass
  - Results from a decrease in plasma volume
    - Copious sweating
    - Vomiting
    - Volume depletion

Charlie: Diagnostics – One day post-treatment

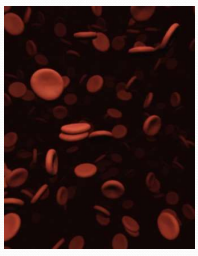
- CBC:
  - WBC 31,800 Stress leukogram
  - HCT 55% after fluid bolus and phlebotomy
- Serum chemistry
  - Total protein 3.0 mg/dl (Albumin 1.1 / globulin 1.9)
  - Normal liver enzymes / creatinine / BUN

Erythrocytosis

- Absolute
  - Caused by an increased total RBC mass (increased RBC numbers)
  - Divided into primary and secondary categories

Charlie: Diagnosis

- Erythrocytosis
  - Definition
    - Abnormally increased packed cell volume (PCV), red blood cell (RBC) count and hemoglobin (Hb) concentration
  - Relative vs. Absolute
  - Previous terminology polycythemia



Erythrocytosis

- Secondary > Primary
  - Response to high serum erythropoietin (EPO)
  - Red cell production is EPO dependent
    - EPO manufactured primarily in the kidneys
    - Acts as a growth factor
    - Stimulates mitotic activity in erythroid progenitor cells / Hb synthesis
    - Stimulates release of reticulocytes from the bone marrow

Normal physiology

- O_2 transport is primary function of the RBC
- Erythroid precursors in bone marrow
  - Primarily colony-forming unit erythroid cells stimulated by EPO > undergo growth and maturation to maintain RBC mass > oxygen to tissues
  - Optimal O_2 delivery ay PCV of 40-45%
    - Species differences – Dachsund, Greyhounds higher values
    - Other factors O_2 dissociation curve, CV status, Hb structure

Secondary erythrocytosis

- Appropriate (persistent hypoxia)
  - High altitude
  - Alveolar hypoventilation
  - Pulmonary disease
  - Cardiac right to left shunts
  - Hyperadrenocorticism
  - Severe obesity
- Inappropriate (without hypoxia)
  - Renal mass (carcinoma, lymphoma), nasal FSA, cecal leiomyosarcoma
  - Pyelonephritis / cysts / hydronephrosis
  - Can be more common

Erythropoiten

- Kidney
  - Primary site of production – renal interstitium
  - Type 1 (stellate) cells – interstitial fibroblasts >> EPO production
    - Proximal convoluted tubule of the deep cortex/outer medulla
    - Oxygen sensors > At this level of cortex, O_2 consumption is high, O_2 tension falls to 40-50 mm Hg >> increased EPO production
  - Type 2 cells – lymphocytic – Ag presentation/expression of cell surface MHC molecules

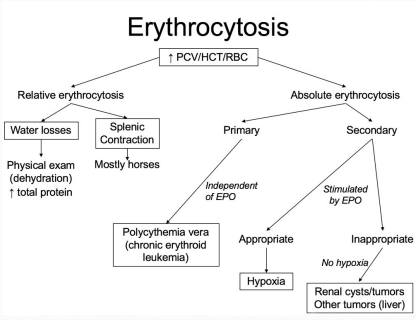
Primary erythrocytosis

- Increased total RBC mass due to an autonomous EPO-independent production of RBC's
- Myeloproliferative disorder
  - Clonal proliferation of neoplastic erythroid stem cells that require little EPO for clonal expansion, growth, differentiation
  - EPO levels low due to lack of negative feedback
- Unknown cause
- In humans called polycythemia vera
  - Canine/feline: Rare neoplastic disease of young-middle aged animals
  - No breed or sex predilection
- Gradual onset, chronic course

EPO

- Heavily glycosylated 34-kD polypeptide hormone
- Hematopoietic growth factor
- Production governed by negative feedback
  - Hypoxia >> increased EPO
  - Increased tissue oxygenation >> decreased EPO
- Half-life (canine) : 6-9 hours
- Only human recombinant EPO (rh-EPO) is commercially available
  - Epogen, Procrit, Amgen
  - Species specific antigenic differences
  - Canaine and feline EPO show 85% sequence homology to human EPO
  - Anti-EPO antibody formation speculated in the cat
  - Impaired iron utilization with long term use ?

Erythrocytosis



Erythrocytosis

- In all cases:
  - Increased RBC mass results in increased blood viscosity and resultant neurologic signs
  - Vascular hindrance / decreased microcirculation / local hypoxia
    - Small vessel / capillary distension
    - Thrombosis / hypoxia / vessel rupture
  - Thrombosis of cortical arteries
  - O_2 consumption and utilization tightly regulated in the brain

Back to Charlie

- Normal thoracic / abdominal radiographs
- Normal chest / abdominal ultrasound
- Normal arterial blood gas
- EPO level
  - 11.28 (5-15 mu/ml)
    - Expect low to normal level with primary
    - Expect high levels with secondary

Erythrocytosis

- Clinical Neurologic Signs
  - Seizures
  - Behavior changes
  - Blindness
  - Ataxia
- Other clinical signs
  - PU/PD / Skin and mm erythema (plethora) / V/D
    - PU/PD theorized to be due to impaired vasopressin release (2 dogs) and decreased concentrating ability
  - Bleeding diatheses (epistaxis, melena, hematemesis)
  - Ophthalmologic lesions

Charlie's serial CBC's

Date	WBC (10)	RBC (m/µl)	HCT (%)
4/27	31.8	8.52	55.0
4/29	41.8	6.61	42.5
5/2	23.3	6.77	43.7
5/6	14.8	7.11	46.1
5/13	7.87	8.34	54.4
6/11	13.5	9.46	60.6
8/1	10.2	10.3	65.0

Erythrocytosis - Diagnosis

- History
- Determination of subcategory of disease
  - Serial evaluation of PCV / Hb concentrations
- Minimal data base (CBC/Chemistry/UA)
  - Measurement of total RBC mass – definitive method for differentiating relative from absolute (I-labeled albumin / isotope tagged autologous RBC's
  - Absolute reticulocyte count higher than 40,000/ul in presence of elevated PCV
- Thoracic/Abdominal radiographs
- Chest/Abdominal ultrasound
- Serial blood gases
- Endocrine testing / EPO levels
- Bone marrow cytology rarely useful – no characteristic erythroid markers for primary erythrocytosis
- Exclusion of hypoxic or neoplastic causes

Erythrocytosis - Treatment

- Relative
  - Intravenous fluids / correction of disease process
- Absolute – Secondary
  - Correct underlying disease process if possible
  - Phlebotomy (10-20 ml/kg serial blood draws)
    - Removal of 20 ml/kg results in an approximate 15% reduction in PCV
    - Careful about hypoproteinemia/hypovolemia
    - Iron deficiency if multiple phlebotomies
      - Approx. 50 mg of iron lost with removal of 100 ml of blood
  - Fluid replacement
    - 0.9% saline, plasma or plasma expanders

Erythrocytosis - Treatment

- Absolute – Primary
  - Phlebotomy – if required every 4-8 weeks, then consider:
  - Hydroxyurea
    - Chemotherapeutic drug
    - Inhibits cellular DNA synthesis (not RNA or Protein synthesis)
    - Reversible bone marrow suppression
    - Dose: 30 mg/kg daily X 7-10 days, then titrate the dose to effect 15 mg/kg daily
    - Repeat CBC's at regular intervals (every 7-10 days, then every 3-4 months when PCV normalized)
    - Nausea, anorexia, vomiting, myelosuppression, sloughing of toenails
    - Cats
  - Radioactive phosphorus 32P – much less common
- Survival possible greater than 6 years

Thor: Physical examination

- Within normal limits, except for thin hair coat and overweight
- Lethargic in the exam room

Charlie: Treatment

Date	WBC (10)	RBC (m/μl)	HCT (%)
8/23	7.4	9.57	61.1
8/30	6.37	8.32	53.1
9/6	7.45	7.23	46.6
10/11	9.42	6.39	43.2

Thor: Neurologic examination

- Mentation: Dull, but appropriate
- CNN:
  - Left head tilt
  - Sustained, non-changing rotary nystagmus with the fast phase to the right
  - Drooping left eye lid and lip
  - Absent menace and blink OS
  - Normal nasal and facial sensation

Case 2:

- Signalment:Thor, 3 year old, MI Rottweiler
- Presenting complaint:
  - Vomiting
  - Balance loss
  - Abnormal eye movements
  - Left head tilt
  - Waxing and waning signs
  - Otherwise healthy

Thor: Neurologic examination

- Gait: Vestibular ataxia
- Postural: Within normal limits
- Motor: Normal strength / reflexes
- Sensory: Within normal limits

Thor: Neurolocalization

- Left CNN VII and VIII neuropathy
- Left peripheral vestibular disease
- Differentials:
  - Infectious / inflammatory
  - Metabolic
  - Neoplastic
  - Degenerative

Hypothyroidism

- Neurologic signs
  - Most common neurologic deficit is generalized paresis or weakness
  - Cranial neuropathies also reported: CNN V, VII and VIII most common
  - Megasophagus / laryngeal paralysis
  - Muscle stiffness / myalgia / muscle wasting
- Systemic signs
  - Lethargy / dry hair coat / anemia / anestrus

Thor: Diagnostics

- CBC / Serum chemistry / UA / Thyroid panel / cholesterol
- Results:
  - CBC: Anemia – normocytic/normochromic
  - Normal serum chemistry
  - Cholesterol: 891 mg/dl

Hypothyroidism - Pathogenesis

- Reduces oxygen consumption/BMR by:
  - Decreasing mitochondrial oxidation capacity
  - Muscle oxidative enzyme activity
  - Glucose uptake
- Decreased #'s of Beta adrenergic receptors on muscle cells
  - Impaired muscle glycogenolysis / glycogen deposition
  - Muscle cramps / fatigability
- Decreased protein turnover / reduced protein synthesis/degradation with net protein catabolism
- Hypercholesterolemia > reduced cholesterolesterase activity/impaired muscle uptake of TG's

Thor: Diagnostics

- Thyroid Panel
  - TT4 (Total T4): 1 (N=5-15 nmol/L)
  - TT3: 0.3 (N=1-2.5-nmol/L)
  - Free T4: 3 (N=12-33 nmol/L)
  - TSH: 58 (N=2-30 nmol/L)
- Diagnosis of hypothyroidism confirmed

Hypothyroidism

- **Pathogenesis**
  - Decreased thyroid hormone is responsible for segmental demyelination and axonopathy
  - Myxedematous compression of the nerves as they exit through the foramina or as they travel through the tissue of the head and neck
  - Both Schwann cell and primary axonal injury
  - Involves central and peripheral nervous system
  - Cerebral atherosclerosis
  - Neuropathic / Myopathic changes in humans
  - Immune-mediated thyroiditis

Hypothyroidism- Pathogenesis

- PNS
  - Excessive amounts of aggregated or diffusely occurring glycogen/glycosaminoglycans in:
    - Cytoplasm of Schwann cells/perineural cells
    - In and around myelinated and unmyelinated peripheral axons
    - Capillaries of humans with hypothyroidism
    - Lamellar bodies/abnormal mitochondria described in Schwann cells
    - Shrunken axoplasm in large diameter myelinated fibers /disintegration of axonal neurotubules & neurofilaments
    - Pathogenesis of how low T4 causes this is uncertain

Hypothyroidism

- Treatment
  - Thyroid supplementation
  - Most times, neurologic signs will improve with therapy
  - May take months
- Back to Thor
  - Signs resolved with supplementation over the next month

Hypothyroidism - Pathogenesis

- CNS
  - In rats: axonal transport is reduced peripheral nerves
    - Supports a reduction in microtubule assembly produced by lack of thyroid hormone
    - This regulation of microtubule assembly known to occur in developing CNS
    - Atherosclerosis: Liu & Patnick

Hyperthyroidism

- Approximately 60% of all hyperthyroid people have clinical evidence of muscular weakness or muscle wasting
- Cats
  - Weakness/fatigue reported less frequently
  - Ventral neck flexion
  - Muscle tremors
  - Generalized weakness
  - Thyrotoxic periodic paralysis (humans)

Hypothyroidism

- Diagnosis
  - CBC – Non-regenerative anemia
  - Serum chemistry – hypercholesterolemia
  - Thyroid panel – Low Free T4 / high TSH level
  - Consistent systemic and neurologic signs
  - Electrodiagnostics – EMG / NCV
  - Nerve / muscle biopsy

Case 3:

- Signalment: Buddy, 8 year old, MC Labrador retriever
- Presenting complaint:
  - When excited, he has small “fits” and muscle fasciculations / more nervous lately
  - Seems weaker, especially when exercising
  - Mouth chomping / seems dazed
  - Progressively worse over 8 months

Buddy: Physical and Neurologic examinations

- Physical exam:
  - Normal except for multiple skin masses
- Neurologic Exam:
  - Mentation
    - Dull, but responsive
    - Focal facial twitching
    - Right head turn episodes

Buddy: Diagnostics

- CBC
- Serum chemistry
- UA and U c/s
- Thoracic and abdominal radiographs

Buddy: Neurologic exam

- CNN: Normal
- Gait: mild proprioceptive ataxia
- Postural: Slow conscious proprioception right hind and left hind
- Motor: Diffuse weakness / leans to the right / Normal myotatic reflexes / muscle fasciculations
- Sensory: Normal

Diagnostics

- CBC / UA – Within normal limits
- Serum chemistry
  - Blood glucose: 36 mg/dl (repeated twice)
  - Immunoreactive insulin (IRI): 37 IU (N=5-20)
- Plan:
  - Surgical exploratory in light of hypoglycemia and high suspicion for insulin-secreting tumor
  - Partial pancreatectomy for pancreatic mass / liver biopsy

Buddy: Neurolocalization

- Diffuse forebrain R >> L
- Differential diagnoses:
  - Metabolic:
    - Hepatic encephalopathy
    - Hypoglycemia
    - Electrolyte disturbance
  - Neoplastic
  - Inflammatory / Infectious

Buddy: Results

- Biopsy results:
  - Pancreatic islet cell carcinoma
  - Liver – Vacuolar degeneration / steroid hepatopathy
- Final diagnosis: insulin-secreting tumor

Insulin-secreting tumor (Islet Cell tumor)

- Insulin-secreting tumors and the resultant hyperinsulinemia interfere with glucose homeostasis
  - Decrease rate of glucose release from liver
  - Increase glucose uptake via insulin-sensitive tissues
  - CNS uses glucose as primary fuel source
  - CNS glucose entry is by diffusion

Clinical signs

- Mirror the pathophysiology
  - Lack of glucose supply to brain (neurogylcopenia)
  - Sympathoadrenal stimulation
- Neuroglycopenia:
  - Weakness / ataxia / behavior changes / seizures / disorientation
- Sympathoadrenal stimulation:
  - Nervousness / muscle tremors / restlessness / hunger

Pathogenesis: Hyperinsulinism

- Results in poor glucose supply for intracellular oxidative processes within neurons
- Neural hypoxia
- Acute hypoglycemia:
  - Affects cerebral cortex / basal ganglia / hippocampus

Diagnosis of hyperinsulinism

- Documentation of normal or low serum blood glucose in the face of an elevated IRI level
- Clinical signs
- Surgical exploration and biopsy

Pathogenesis: Hyperinsulinism

- Chronic hypoglycemia
  - Peripheral nerve degeneration / muscle oxidative metabolism changes
  - CNS effects due to release of counterregulatory hormones
    - Catecholamines / Glucagon

Treatment: Hyperinsulinism

- Surgical excision
  - Treatment of choice
  - Liver biopsy since high metastatic potential
  - Complications
    - Pancreatitis
    - Diabetes mellitus
  - Prognosis: 350 days (10% die perioperatively, 15% survive > 2 years)

Treatment: Hyperinsulism

- Medical
  - Combined with surgery or if surgery is not an option
  - Prednisone
    - 0.5 mg/kg divided BID PO
    - Promotes hepatic gluconeogenesis
    - Decreases peripheral glucose utilization

Medical Treatment: Hyperinsulinism

- Dietary therapy:
  - Feed canned or dry food in 3 to 6 small meals daily (high carbohydrate, low simple suger)
  - Avoid soft, moist foods
  - Avoid foods containing mono or disaccharides
  - Limit exercise

Treatment: Hyperinsulinism

- Diazoxide (limited availability)
  - Non-diuretic benzothiadiazide
  - Inhibits insulin secretion
  - Inhibits glucose uptake by tissues directly
  - Stimulates hepatic gluconeogenesis / glycogenolysis
  - Dose: 10-60 mg/kg divided BID
  - Cost prohibitive / Side effects

Medical Therapy: Hyperinsulinism

- Streptozotocin
  - Chemotherapeutic
  - Must be administered in hospital
  - Side-effects
- Mean survival with medical management only: 60 days

Medical Treatment: Hyperinsulinism

- Octreocide (Sandostatin)
  - Somatostatin analogue
  - Long duration of action / increased potency / excellent bioavailability when given SQ
  - Responsiveness depends on # of receptors on tumor cells
  - Dose: 10-40 µg SQ 2 to 3 times daily

Case 4:

- Cody
- 5 year old, MC, Labrador retriever
- Presenting neurologic complaint:
  - Inability to stand, extremely weak

Cody: History

- Non-specific history of 2 weeks duration
  - Anorexia
  - Difficulty rising
  - Intermittent vomiting
  - Shivering and trembling
- No toxin exposure
- Indoor dog, well-supervised

Cody: Neurolocalization

- Diffuse neuromuscular disease
- DDx:
  - Neuropathy
  - Polyradiculoneuritis
  - Myopathy
  - Atypical myasthenia gravis
  - Underlying metabolic illness

Cody: Physical examination

- Bradycardia
- Evidence of weight loss
- Dehydrated
- Diffuse weakness

Cody: Diagnostic Plan

- CBC
  - Within normal limits except for increased TP
- Serum chemistry
  - Na 120 (141-154)
  - K 9.4 (3.9-5.3)
  - Cl 95 (107-124)
  - Mild azotemia

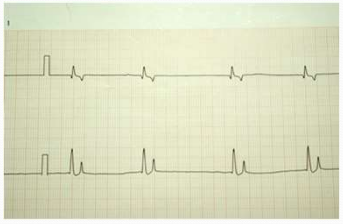
Cody: Neurologic examination

- Mentation: within normal limits
- CNN's: Within normal limits
- Gait: Non-ambulatory, tetraparetic
- Postural: Within normal limits
- Motor: Non-ambulatory tetraparetic
  - 0-1+ hyporeflexia all limbs
  - Lower motor neuron signs

Cody: Further diagnostics

- ECG
- ACTH Stimulation test
  - Pre: < 1.0 µg/dl
  - Post: < 1.0 µg/dl
- Final diagnosis: Hypoadrenocorticism

ECG: Hypoadrenocorticism



Hypoadrenocorticism: Pathophysiology

- Electrolyte levels are tightly regulated in the CNS and the PNS
- Impairment of muscle CHO metabolism, water and electrolyte balance, muscle blood flow, adrenergic sensitivity
- Depletion of muscle intracellular potassium, decreased membrane Na-K ATP activity, diminished Beta adrenergic stimulation of Na-K pump
- Sudden shifts and imbalances can result in dramatic neurologic clinical signs
- Most of these clinical signs are reversible with the appropriate therapy
- Atypical Addison's
  - Described in 11-26% of dogs
  - Deficiency of glucocorticoids alone

Cody: Hypoadrenocorticism

- Common presenting clinical complaints
- Common presenting neurologic clinical complaints:
  - Generalized weakness
  - Shivering
- Not so common presenting neurologic clinical complaints:
  - LMN tetraparesis, diffuse hyporeflexia, may affect pharyngeal/laryngeal musculature

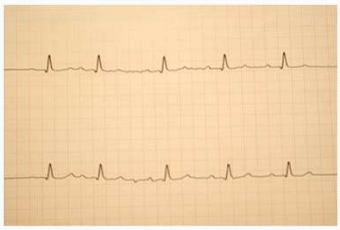
Hypoadrenocorticism: Therapy

- Acute crisis:
  - Reverse the volume depletion due to Na loss
  - 0.9 % NaCl / Glucocorticoids
  - Time
- Chronic:
  - Fludrocortisone acetate (Florinef)
  - DOCP – Desoxycorticosterone pivilate – (Percortin)

Hypoadrenocorticism: Pathophsiology

- Peripheral nervous system:
  - Weakness
  - Paralysis
  - Loss of deep tendon reflexes
- CNS:
  - Mentation changes
  - Confusion

ECG: Post-treatment



Points to Remember

- Thorough physical and neurologic examinations are essential
- Use appropriate diagnostics to determine the underlying condition
- Assume nothing .....
- "Life is a long lesson in humility"
  - J. M. Barrie

Questions ?