Toxic Differentials of Central Nervous System Excitation in Small Animals

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The objectives of this article are to give a broad overview of toxicants which cause CNS excitation in small animals and to assist clinicians in generating a toxic differentials list. A supplementary table located on our website provides information on choosing the appropriate specimens and provides a guide for testing that is available at DCPAH.

The CNS is a common target for toxicants and interference with normal activity of the CNS is a leading cause of death in small animals. The CNS is particularly vulnerable to toxicant-induced disease because of its high energy demand and high dependence on aerobic respiration. Clinical signs of CNS excitation include increased anxiety, hyperactivity, muscle tremors, and seizures. These signs may be accompanied by tachycardia, hypertension, fever, and rapid respiration. Toxicants may induce CNS excitation primarily by: 1) interference with neurotransmission; 2) interference with oxygen or glucose delivery and glucose utilization by inhibiting the TCA cycle.

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Toxicants which induce CNS excitation via multiple mechanisms. Clinicians are advised to

(Toxic Differentials continued on page 2)
Case Study: Severe Nonregenerative Anemia in a Dog

By: DCPAH Clinical Pathologists

Signalment:
5-year-old male Polish Tatra Sheepdog.

History:
Idiopathic epilepsy controlled with phenobarbital; progressive lethargy and pallor for 1 1/2 wks; unable to stand; referred for transfusion.

Physical Exam:
Marked pallor; difficulty rising; painful hips.

Major CBC Findings:
Normocytic normochromic nonregenerative anemia (Hct = 15%; reticulocyte concentration = 25,900/µL).

Other Initial Laboratory Findings:
No major abnormalities noted on chemistry, hemostasis, and urine profiles.

Bone Marrow Aspirate:
Hypercellular particles with adequate iron, decreased myeloid to erythroid (M:E) ratio, and an expanded erythroid series with relatively few late-stage precursors and reticulocytes (Figure 1); many macrophages contained basophilic degraded cellular material and few contained late-stage erythroid precursors (Figure 2).

Diagnosis:
Marrow-directed immune-mediated anemia (MIMA) characterized by ineffective erythroid hyperplasia, decreased late-stage erythroid precursors, and evidence of phagocytic destruction of late-stage precursors.

Treatment:
Fluids, packed red blood cells, prednisone, azathioprine, famotidine, buprenex for joint pain, aspirin to prevent thrombosis, and phenobarbital.

Outcome:
Azathioprine was discontinued one month later. Severe anemia recurred one year from initial presentation, and immunosuppressive therapy again resulted in remission.

Comment:
MIMA is the single most common diagnosis for severe persistent unexplained nonregenerative anemia in our canine referral population. Bone marrow examination and concurrent CBC are needed for the diagnosis. Drs. Scott (DCPAH) and Jutkowitz (Emergency Critical Care, Veterinary Teaching Hospital) are currently characterizing the hematologic and clinical findings in these dogs. Immunosuppressive therapy appears to resolve the anemia, though more slowly than in dogs with immune-mediated hemolytic anemia and destruction of mature erythrocytes. Some dogs with MIMA have developed other immune-mediated cytopenias or a recurrent bout of MIMA.
**Frequently Asked Questions in Clinical Pathology**

By: DCPAH Clinical Pathologists

Why might my patient’s fasting bile acid concentration be higher than the postprandial bile acid concentration?

**Bile Acid Basics:**
Measurement of fasting and postprandial bile acids is a relatively sensitive and easily performed screening test to detect hepatobiliary disease or portosystemic shunts (PSS). Normally, after a meal is ingested, the gallbladder releases bile acids into the intestines. Later, bile acids are absorbed into the portal circulation and most are removed by the liver. Increased bile acids in the systemic circulation occur if there is decreased removal from portal circulation (e.g., hepatic failure, PSS) or decreased biliary excretion (e.g., hepatic or post-hepatic cholestasis).

**Case Example:**
A 5-year-old neutered male dog had a nine-month history of seizures which were increasing in frequency. Physical examination was unremarkable. Serum biochemical and CBC results were within reference limits, except for the following:

<table>
<thead>
<tr>
<th>Bile Acids</th>
<th>Patient</th>
<th>Ref. Int.</th>
</tr>
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<tbody>
<tr>
<td>Fasting</td>
<td>34.4 μmol/L</td>
<td>0.5-8.7</td>
</tr>
<tr>
<td>Postprandial</td>
<td>23.0 μmol/L</td>
<td>0.5-23.4</td>
</tr>
</tbody>
</table>

This pattern of bile acid results is common. Review of 470 canine bile acid profiles submitted to DCPAH from July 15, 2009 through July 14, 2010 revealed that 109 (23%) had higher fasting than postprandial bile acid concentrations, and 76 of these profiles had values within reference limits or only mildly increased. This pattern may occur when: 1) gallbladder contraction is stimulated by something other than ingestion of food, 2) the dog ingests something unbeknownst to the owner or veterinarian, or 3) sample tubes are mislabeled. The fasting value may exceed the upper reference limit for the postprandial sample because of variations in gallbladder contraction (e.g., the fasting value does not reflect baseline concentration) and in time from contraction to sampling.

Interpretation of bile acid results can be challenging and should include consideration of history, physical examination, and other diagnostic findings (e.g., serum biochemical profile, imaging of the liver). Values that are only mildly increased, as in this dog, may or may not be caused by hepatobiliary disorders or PSS. This dog had no other findings to support hepatobiliary disease or PSS (baseline plasma ammonium concentration and hepatic ultrasound were within normal limits). The seizures were felt to be nonhepatic in origin and the dog responded to anticonvulsant drugs.

Why should I send slides along with fluid for cytologic examination? Is there an additional charge?

**Fluid Submission Basics:**
It is best to submit slides made immediately after fluid collection (see http://www.animalhealth.msu.edu/News/2008_Fall.pdf for slide preparation tips) because cells deteriorate during transit to the laboratory, particularly if fluids lack sufficient protein to stabilize cell membranes (e.g., washes, cerebrospinal fluid). Cellular deterioration makes it difficult to assess cell details and even to determine cell types. Moreover, contaminating bacteria may proliferate and be phagocytized in vitro during transit, making it difficult or impossible to differentiate sepsis from contamination.

When smears are submitted with fluid, the submitted smears and smears made in our laboratory from the fluid are examined. There is no additional charge to review the submitted smears.

**Case Example:**
The client submitted direct smears, concentrated smears made from sediment that was resuspended after centrifugation of an aliquot of the wash fluid, and tracheal wash fluid from a two-month-old male horse that was dyspneic and febrile. Auscultation revealed wheezes and crackles in all lung fields. The samples arrived two days after collection. Concentrated smears made at DCPAH from the submitted fluid contained large numbers of lysed and deteriorated nucleated cells (Figure 1). Most could not be identified as to type. There were many extracellular bacteria. Intracellular bacteria were not confirmed. In contrast, the submitted concentrated smears had numerous neutrophils (Figure 2), many containing intracellular bacteria. Based upon the submitted smears, a diagnosis of septic neutrophilic inflammation was possible.

**FIGURE 1:** Concentrated smear made from two-day-old tracheal wash fluid. Lysed nuclei from deteriorated cells and extracellular bacteria. Wright stain, 100× objective.

**FIGURE 2:** Concentrated smear of the same tracheal wash fluid made soon after collection. Note the intact neutrophils and the intracellular bacteria. Wright stain, 100× objective.
DCPAH Fee Increase

Effective September 1st, 2010, DCPAH test fees will be increased. An updated schedule for most of the services provided by DCPAH is included with this newsletter. However, please note that the most current fee information for all the tests we offer is always available to you online by clicking either the “Fee Schedule” or “Available Tests” link on the main page of our website (www.animalhealth.msu.edu).

Fee increases are a necessary but unwelcome change for all of us. Please remember that we attempt to price our services fairly and reasonably for our clients and that DCPAH has never charged either accession or out-of-state fees for any service.

A few of our clients have expressed concern that we publish our fees on our website. We do this to remain competitive with other diagnostic service providers and not for use by animal owners. However, occasionally we hear from one of our clients that an owner has complained because he or she expected to pay only the cost of the test that was posted on our fee schedule. If this should happen in your practice, please remind your client that your fee included not only the cost of the test but also your professional services (obtaining the sample, shipping costs, and treatment recommendations based on the test results). We have added a disclaimer to our fee schedule that we hope will deter animal owners from raising this issue with you.

We value and appreciate your business and hope you will continue to choose DCPAH for your veterinary diagnostic needs.

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We have the answer if your clinic is looking for an economical and effective way to send us specimens quickly and safely.

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