

THOSE PESKY ELEVATED LIVER ENZYMES

WHAT ARE THEY AND WHAT DO THEY MEAN?

“So, what’s the deal with elevated liver enzymes in Scotties?” It was my colleague and good friend on the phone. She went on to describe marked elevations of specific liver enzymes in an otherwise healthy, seven-year old Scottie bitch. My friend had proceeded with all the standard tests to find an answer for her client, but in the end, a definite diagnosis remained elusive. It was an unsatisfying and frustrating conclusion, to say the least.

Having had no direct experience with this problem at the time, I was of little help to my friend. But since then, after several phone calls, letters, and e-mail postings, I have discovered that there are multiple cases of unexplained elevations of liver enzymes in Scotties, and that there is also a great deal of confusion and speculation on just what is going on. I thought it might be helpful to explain in some detail just what these enzymes are, where they originate and what they mean when they are elevated. But first, a bit of liver anatomy and physiology will be useful.

Weighing in at about one pound in a 27 pound dog, the liver nestles neatly up against the diaphragm, hovering over the entire abdominal contents in a position befitting its essential role: that of protector, primary provider, producer, and major recycler. It is truly the king of metabolic and digestive function and its list of duties is impressive:

- Receipt of all blood flow from the gut via the portal vein;
- Production and metabolism of essential proteins such as albumin and clotting factors;
- Center of carbohydrate and fat metabolism;
- Center of bile acid, ammonia, drug and hormone metabolism;
- Production and storage of bile;
- The major detoxification center in the body;
- Center of the reticuloendothelial (RES) system, essential in recycling worn out red cells as well as cleaning up, stockpiling, and sweeping out.

At the heart of all of this activity is the hepatocyte, the liver cell, a tiny hexagonal factory fitting up against its neighbors in an efficient and miraculous pattern to form the hepatic lobule. As revealed under microscopic power, the design consists of somewhat irregular rooms, crooked hallways, larger channels and finally huge vessels delivering food and toxins from the intestine in one corner, receiving oxygen from the heart and lungs in another corner, draining away the venous, spent blood at the very center, and collecting and shunting bile into the large ducts to aid in digestion. The liver has the unique power of regeneration, is capable of forgiving most of the excesses in our lives, but asks little in return. And we just boil and bake the stuff for bait in the ring!

Now, where do those “enzymes” fit into this picture? And what is an enzyme anyway?

An enzyme is a protein, a molecule of a specific chemical structure, synthesized inside of cells and designed to be involved in certain complex biochemical reactions inside or outside of the cell. When the hepatic factory is humming along smoothly, all biochemical processes essential to the life of the cell also proceed normally. However, if you insult the hepatocyte with a drug or toxin, with the fender of a Toyota Corolla or the kick of a pony, with the backflow of venous blood from a failing heart, with infectious agents from the bowel or the insidious invasion of cancerous cells, then the factory may grind to a halt and the cell may swell, rupture and die. Thus, certain enzymes will be released into the circulation in levels higher than are normally found, and the veterinarian can gain a huge amount of information when the serum chemistry is studied.

The most common enzymes your veterinarian may report are ALT (Alanine Aminotransferase) and ALP (Alkaline Phosphatase). Of course there are many others, but these two are the flags we look for when first suspecting a liver disorder. ALT is an intracellular enzyme and is liver specific in the dog. When we see elevations of ALT, we know that there has been some degree of cell membrane damage to allow leakage of this enzyme into the circulation. This enzyme's half-life is 48 hours, meaning that one half of the enzyme should be gone in 48 hours. If we find on subsequent blood work that in fact the ALT levels have decreased by half, then we know this liver injury/insult was a one-time event, and healing is underway. If the ALT levels continue to rise, there is ongoing injury/insult to the liver and the prognosis is darkened considerably. The most common causes for marked elevations of ALT are chronic active hepatitis, primary liver cancer, hepatic necrosis (meltdown), pancreatitis, severe anemia, ischemia (loss of blood flow and oxygen), sepsis and toxemia. As you may guess, these are all pretty nasty problems and, in general, high elevations of ALT make us all a little nervous.

High elevations of ALP, on the other hand, usually carry a less dire prognosis, but this enzyme is more difficult to interpret. The reason for the complexity is that ALP is not liver specific but is found in many tissues including bone, kidney, placenta, intestine, and of course liver. All of these variations on the ALP theme are known as "isoenzymes", but only the isoenzymes derived from bone and liver have a half-life long enough to be clinically significant, *i.e.* detectable in a blood test. In the liver, ALP is produced by cells lining the narrow canals through which bile normally flows. Increases in ALP in the blood indicate bile flow obstruction due perhaps to accumulation of fats, bile stones plugging up the ducts, perhaps severe infection or cancer. ALP may also be elevated in response to certain drugs, such as anticonvulsants and barbiturates, with or without actual detectable changes in liver function.

To make matters even more confusing, there is a steroid induced ALP isoenzyme (we'll call s-ALP) which is also produced in the liver but is distinguishable from ALP induced by bile flow obstruction. Dogs are uniquely very sensitive to the effects of steroids, and s-ALP may be induced to very high levels with either naturally occurring steroid hormones or those that we administer. Causes for naturally occurring steroid release include stress (pregnancy, surgery, cancer) and Cushings disease. But steroids that we give an animal can also have a huge effect. Consider the very common use (and possibly over use) of steroids in the veterinary profession today. Any steroid medication including

injections (long and short duration), “itch pills”, topical medications such as eye or ear drops or skin cream can all cause an elevation of the s-ALP for weeks and even months after the medication is gone.

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Typically, a dog with serious liver disease will exhibit some if not all of a variety of depressing and debilitating symptoms including vomiting, diarrhea, increase in thirst and urination, weight loss, lack of appetite, bleeding abnormalities, a sickly yellow cast to the eyes and gums, lethargy, and possibly seizures. The blood work will reveal an assortment of elevated enzymes and other parameters that will underscore what we already suspect- the liver is very sick.

But what about cases like the healthy, normal middle-aged Scottie who came to my colleague’s clinic for routine teeth cleaning and a high ALP was found on preanesthetic blood work? There were no other abnormalities. An appropriate next step would be to postpone the anesthesia for 6-8 weeks and recheck the blood at that time. If the ALP is still elevated, then other tests should be performed including bile acid test to check on liver function, blood tests to rule out Cushings disease, abdominal radiographs and possibly ultrasound concentrating on the liver and adrenal glands. In some cases, a liver biopsy may be indicated. Hidden disease may be found with a thorough search, but in some cases, no explanation is found.

So what is the deal?

Dr. Gary Block, a veterinary internal medicine specialist in Warwick, Rhode Island became very interested in elevated ALP in Scotties and did some early investigative work on four closely related dogs with ALP values ranging from 400-2000 IU/L. These dogs were all healthy and happy pets that tested negative for Cushings disease and showed no other abnormalities on blood work at that time. The liver biopsies showed moderate changes typical of steroid effects, although steroid use in these dogs was reported to have been minimal if at all. Dr. Block was working with Dr. Walter Hoffman at the University of Illinois to examine the blood samples from these Scotties and separate out the isoenzymes. According to Dr. Block, it was Dr. Hoffman’s impression that the predominant isoenzyme was the steroid induced ALP, and that this finding pointed to some degree of chronic stress in these animals. But where did the stress originate? Was there an underlying and more hidden process that had only begun to affect the system? Could the stress induced ALP be a flag for disease to be diagnosed at a much later date, such as cancer, somewhere in the body? Or, as Dr. David Twedt suggests in his excellent article “Interpreting increased liver enzyme values in senior patients”, are there more complex and not fully understood changes in the adrenal glands that produce many different steroids in the body, leading to unexplained but harmless increases in ALP in the liver? And, is it possible that there is a genetic factor at play?

Clearly, there are a lot of questions to be answered. Stay tuned for future developments.

SOURCES

- Block, Gary, DVM: telephone conversation. Warwick, RI, August 1999.
- Couto, Guillermo, DVM et al: Hepatobiliary and exocrine pancreatic disorders. In: *Small animal internal medicine, 2nd edition*. St. Louis, MO: Mosby, Inc, 1998; 475-570.
- Ettinger, Stephen J, DVM, et al: Diseases of the liver and their treatment. In: *Textbook of veterinary internal medicine, 3rd edition*. Philadelphia, PA: WB Saunders Co., 1989; 1479-1527.
- Miller, Malcolm, DVM, PH.D: The digestive apparatus and abdomen. In: *Miller's anatomy of the dog, 2nd edition*. Philadelphia, PA: WB Saunders Co, 1979; 492-501.
- Selzer, Richard, MD: Liver. In: *Mortal lessons- notes on the art of surgery*. New York, NY: Simon and Schuster, 1976; 62-77.
- Tamms, Todd DVM: Diseases of the liver. In: *Handbook of small animal gastroenterology*. Philadelphia, PA: WB Saunders Co, 1996; 371-459.
- Twedt, David, DVM & Dipl. ACVIM: Interpreting increased liver enzyme values in senior patients. *Vet Econ, supp*, 29-37; unknown vol, issue and date.