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2024.09

BASIC APPROACH TO EVALUATE HEPATIC & RENAL FUNCTION

Presented at the Indian VETopia on February 21, 2024 in India

Dr. Masahiko Sato

DVM, PhD, DACVIM(SAIM), DAiCVIM(IM),
Chief of Internal Medicine Service at the Veterinary Specialists Emergency Center in Japan

Introduction

Liver and kidney diseases in dogs are difficult to diagnose because patients often present with nonspecific symptoms such as lethargy, decreased appetite, and vomiting, making it difficult to estimate the cause of the disease from the symptoms alone. In addition, elevated liver enzymes and kidneys values in blood chemistry test results can be seen in diseases other than liver and kidney disease, so a comprehensive diagnosis that includes evaluation of other organs is necessary to correctly interpret the results of such blood tests. Important considerations when evaluating the liver and kidneys are shown in this article.

Liver

When interpreting blood chemistry test results for the liver, it is necessary to evaluate liver damage and liver function separately. Since the liver is an organ with large reserve capacity and regenerative capacity, the presence of liver damage does not necessarily mean that liver function is impaired. Liver damage should be evaluated separately for (1) hepatocellular damage and (2) impaired biliary flow. The differential diagnosis depends on which is the main abnormality. The blood chemistry test parameters for each are shown in Figure 1. ALT and AST, indicators of hepatocellular damage, are often elevated outside of primary liver disease and must be evaluated in conjunction with other blood chemistry test results for their interpretation. Since elevations in ALT level can also occur secondary to cardiovascular diseases, endocrine disorders, gastrointestinal diseases, and systemic inflammation, a combination of medical interview, physical examination, blood chemistry tests, urinalysis, and imaging examinations are necessary to know the cause of elevated liver enzyme levels.

There are several parameters for evaluating liver function (**Figure 1**). The bile acid is a highly sensitive parameter to detect decreased liver function in liver diseases that progress slowly, such as chronic hepatitis (**Figure 2**). The bile acid level is elevated in the presence of ① decreased liver function, ② vascular abnormalities (e.g., portal vein shunts), and ③ cholestasis and is a useful marker to detect early-stage liver dysfunction if neither ② nor ③ are present. Measuring the bile acid before and 2 hours after a meal can increase the sensitivity.

Blood work to evaluate liver damage and function — Fig. 1

Liver damage

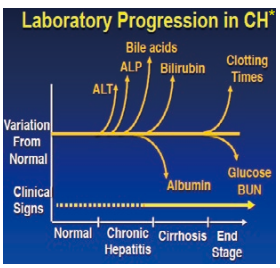
Damage to hepatocytes: ALT, AST

Cholestasis (impaired biliary flow): ALP, GGT, T-bil, T-cho, Bile acids

Liver function

Bile acids, T-cho, T-bil, ALB, Glu, NH_3, BUN, Clotting factors

Progression of liver dysfunction — Fig. 2

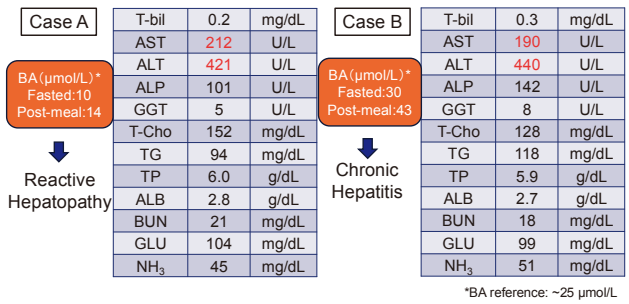


*CH: chronic hepatitis

Case study (1): Asymptomatic dogs with elevated liver enzymes

Case A and B dogs were asymptomatic, but their blood chemistry test results showed elevated liver enzyme levels at their health checkups. The blood chemistry test results were similar in Case A and B. The pre- and post-prandial bile acid levels in Case A were in the normal range, but the bile acid levels in Case B were abnormal (**Figure 3**). The final pathological diagnosis was reactive liver damage secondary to gastrointestinal disease in Case A, whereas Case B was chronic hepatitis. Thus, even with the same elevated liver enzyme levels, as in Case B, elevated liver enzyme levels with decreased liver function are more suspicious of primary liver disease requiring therapeutic intervention, making the measurement of bile acids, a highly sensitive test to detect decreased liver function. In addition, as in Case A, elevated liver enzyme levels can also be seen with extrahepatic disease, so a systemic evaluation for extrahepatic disease is necessary before performing a liver biopsy.

Case study (1): Blood chemistry test results in Case A and B — Fig. 3



Case study (2): 8 years old, spayed female, Yorkshire Terrier

Progress: Intermittent soft stools and weight loss over the past approximately 3 months
Physical examination: Normal Temperature, Pulse Rate, and Respiration Rate(TPR), Body Condition Score (BCS) 3/9, Moderately decreased muscle mass, No other special notes

Blood test results:

	Case		Ref range
Ht	37	%	37~55
Neu	8.5	x10³/μL	3~1.15
PLT	280	x10³/μL	200~500
TP	4.2	g/dL	5.0~7.2
ALB	2.0	g/dL	2.6~4.0
GLB	2.2	g/dL	1.6~3.7
GLU	92	mg/dL	75~128
BUN	24	mg/dL	9.2~29.2
CRE	1.2	mg/dL	0.4~1.4
T-BIL	0.2	mg/dL	0.1~0.5

	Case		Ref range
ALT	382	U/L	17~78
ALP	110	U/L	~89
GGT	2	U/L	5~14
T-CHO	91	mg/dL	110~312
CPK	82	U/L	49~166
Ca	9.1	mg/dL	9.3~12.1
NH_3	38	μg/dL	16~75
PreBA*	5	μmol/L	~25
PostBA	8	μmol/L	~25

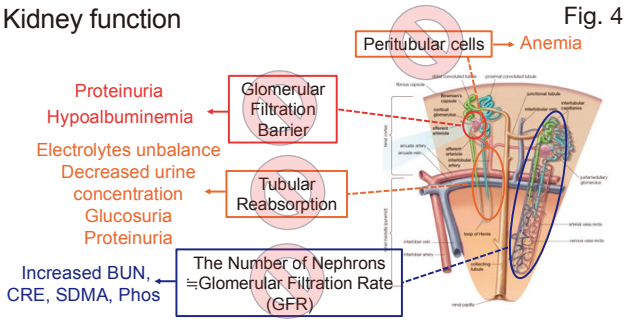
*Bile Acids

Interpretation of blood test results: Abnormal values are shown in red; elevated liver enzyme levels, mainly ALT, and low ALB and cholesterol levels could indicate liver damage or liver dysfunction, but is it right to proceed to liver biopsy as primary liver disease for this case? What is of interest is the bile acid levels, and since the bile acids are in the normal range, low ALB and cholesterol levels are most likely caused by other factors aside from liver dysfunction. Typical differentials for low ALB level, besides liver dysfunction, are protein-losing enteropathy and protein-losing nephropathy. In this case, urinalysis was negative for urinary protein, thus protein-losing nephropathy was ruled out. Since hypocholesterolemia is also seen in protein-losing enteropathy, fecal examination, ultrasonography, and cobalamin measurement were performed in this case to investigate gastrointestinal disease. Since intestinal lymphangiectasia and chronic enteropathy were suspected, the diet was changed to a low-allergen diet. ALB level was elevated to 2.8 g/dL and ALT level was decreased to the normal range thereafter. Since elevated liver enzyme levels can also occur secondary to diseases other than liver disease, such as gastrointestinal diseases, that is a reactive liver damage, comprehensive examination and evaluation are necessary to avoid misinterpretation of elevated liver enzyme levels.

Kidney

To evaluate kidney function, generally used blood chemistry tests such as BUN, CRE and SDMA are used as markers for glomerular filtration rate (GFR). But since the kidney function includes the glomerular filtration barrier, tubular reabsorption of water and electrolytes, and production of erythropoietin, etc., a comprehensive evaluation is needed, not only by blood chemistry tests but also by urinalysis. As an evaluation of the glomerular filtration barrier, it is also important to assess the presence or absence of urinary protein and hypoalbuminemia, and as an evaluation of the tubular function, it is important to check for the presence or absence of urinary protein, urinary glucose, and electrolyte levels in the blood. Evaluation of CBC is also necessary because anemia occurs as chronic kidney disease (CKD) progresses (**Figure 4**).
There are various causes leading to CKD (**Figure 5**) and treatment varies depending on the cause and stage of the disease, so blood tests, urinalysis, imaging examinations, and blood pressure measurements are performed to properly evaluate condition of the patients.

Kidney function — Fig. 4



A variety of causes for CKD — Fig. 5

- Congenital: Renal hypo/dysplasia, Polycystic Kidney Disease, Inherited glomerulonephropathy etc.
- Acquired: Persistent dysfunction after acute kidney injury
  Glomerular Disease: ICGN vs Non-ICGN (dogs)
  Tubulo-interstitial Disease (cats) etc.

Case study (3): Elevated BUN and CRE levels with chronic polyuria and weight loss

Case A and B dogs presented to the veterinary clinic with chronic polyuria and weight loss, and blood chemistry test results showed elevated BUN and Creatinine levels (**Figure 6**). Case B was also found to have abnormalities such as low ALB and high cholesterol levels. Urinalysis revealed no significant abnormalities in Case A, but severe proteinuria was detected in Case B, with a high urine protein creatinine ratio of 8.9 (**Figure 7**). In Case B, the glomerular filtration barrier was thought to be abnormal, and glomerular disease was suspected as the cause of the kidney disease, and renal biopsy would have to be considered depending on further testing. If you evaluate only BUN and CRE, you cannot notice any other abnormalities and the difference in the underlying disease between Cases A and B, so when assessing kidney function, it is important to perform not only blood chemistry tests but also urinalysis.

Case study (3): Blood chemistry test results in Case A and B — Fig. 6

- PUPD, weight loss and intermittent vomiting for the past 1 ~ 2 months

Case A				Case B			
	BUN	48	mg/dL		BUN	51	mg/dL
	CRE	2.2	mg/dL		CRE	2.4	mg/dL
	P	6.2	mg/dL		P	5.6	mg/dL
	Ca	10.1	mg/dL		Ca	8.1	mg/dL
	TP	6.3	g/dL		TP	5.3	g/dL
	ALB	2.9	g/dL		ALB	1.5	g/dL
	GLB	3.4	g/dL		GLB	3.8	g/dL
	T-cho	185	mg/dL		T-cho	450	mg/dL
	Na	146	meq/L		Na	144	meq/L
	K	4.7	meq/L		K	4.2	meq/L
	Cl	111	meq/L		Cl	114	meq/L

Case(3): Urinalysis results in Case A and Case B — Fig. 7

- PUPD, weight loss and intermittent vomiting for the past 1 ~ 2 months

Case A			Case B		
	USG	1.020		USG	1.018
	Pro	+		Pro	+++
	Glu	-		Glu	-
	Blood	-		Blood	-
	Bil	-		Bil	-
	Ketone	-		Ketone	-
	WBC	0/hpf		WBC	2/hpf
	RBC	3/hpf		RBC	5/hpf
	Casts	-		Casts	-
	Bacteria	-		Bacteria	-

UPC 0.4 → Non-glomerular

UPC 8.9 → Glomerular

A comprehensive evaluation is also required because elevated BUN and CRE levels often occur because of causes other than the kidneys.

Case study (4): Elevated BUN and CRE levels with acute vomiting and lethargy

Case A and B dogs presented to the veterinary clinic with acute vomiting and lethargy, and elevated BUN and CRE levels were found (**Figure 8**). Since the causes of acute kidney injury (AKI, Azotemia) are diverse, including dehydration, kidney intrinsic damage, and urinary tract obstruction (**Figure 9**), evaluation of kidney parameters alone will not get to the cause of the disease. Urinalysis and imaging examinations must first be performed to evaluate for dehydration and urinary tract obstruction. There were no imaging abnormalities suggestive of urinary tract obstruction in either Case A or B. On urinalysis, Case A had decreased urine specific gravity (USG) level and the appearance of proteinuria, glucosuria, and granular casts, strongly suggesting renal tubular damage and intrinsic AKI. In contrast, Case B did not have decreased USG and any findings suggestive of renal tubular damage, suggesting azotemia due to decreased circulating blood volume rather than renal intrinsic damage (**Figure 10**). A comprehensive blood chemistry test in Case A showed findings suggestive of inflammation, hypocalcemia, and elevated lipase level, and the imaging examination showed enlarged pancreas and peripancreatic ascites, suggesting the presence of acute pancreatitis as the cause of AKI (**Figure 11, 12**). On the other hand, in Case B, dehydration was suspected as the cause of azotemia based on high total protein and USG levels, and hypoadrenocorticism was suspected based on high Ca level and low Na/K ratio, so an ACTH stimulation test was performed and hypoadrenocorticism was confirmed (**Figure 13**). Thus, the causes of elevated BUN and CRE levels are diverse, and a comprehensive examination is necessary to properly evaluate azotemia.
As a further exercise in the interpretation of azotemia, one case study is given below.

Case study (4): Blood chemistry test results in Case A and B — Fig. 8

- Acute vomiting and lethargy for 2 days

Case A				Case B			
BUN	84	mg/dL		BUN	98	mg/dL
CRE	3.8	mg/dL		CRE	3.1	mg/dL
P	6.8	mg/dL		P	5.5	mg/dL
Ca	7.8	mg/dL		Ca	13.2	mg/dL
TP	6.2	g/dL		TP	8.1	g/dL
ALB	2.5	g/dL		ALB	4.3	g/dL
GLB	3.7	g/dL		GLB	3.8	g/dL
T-cho	185	mg/dL		T-cho	185	mg/dL
Na	140	meq/L		Na	130	meq/L
K	3.1	meq/L		K	5.8	meq/L
Cl	108	meq/L		Cl	101	meq/L

Classification of AKI (Azotemia) — Fig. 9

Physical Exam, Blood work, urinary exam, Response to Fluids → Imaging

Hypovolemic (Pre-renal)	Intrinsic Renal	Obstruction (Post-renal)
Dehydration	Drug/Toxins	Stone/Plugs
	Infection	Stricture
	Tumor	Tumor
	Inflammation/ischemia	

Case study (4): Ultrasound test and urinalysis results in Case A and B — Fig. 10

- Acute vomiting and lethargy for 2 days

Case A		Case B	
AUS* No renal abnormality → Intrinsic AKI		AUS* No renal abnormality → Hypovolemic AKI	
USG	1.015	USG	1.032
Pro	++	Pro	+/-
Glu	+	Glu	-
Blood	-	Blood	-
Bil	-	Bil	-
Ketone	-	Ketone	-
WBC	2/hpf	WBC	1/hpf
RBC	5/hpf	RBC	2/hpf
Casts	Granular	Casts	-
Bacteria	-	Bacteria	-

*AUS: abdominal ultrasound

Case study (4): Blood chemistry test results in Case A — Fig. 11

- Acute vomiting and lethargy for 2 days

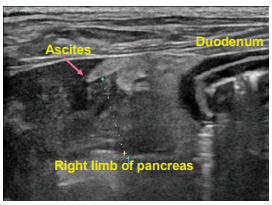
Case A

BUN	84	mg/dL	Ht	38	%
CRE	3.8	mg/dL	Seg	23,000	/μL
P	6.8	mg/dL	Band	100	/μL
Ca	7.8	mg/dL	Lym	580	/μL
TP	6.2	g/dL	Plt	20,0000	/μL
ALB	2.5	g/dL			
GLB	3.7	g/dL	ALT	120	U/L
T-cho	185	mg/dL	ALP	210	U/L
Na	140	meq/L	T-bil	0.2	mg/dL
K	3.1	meq/L	LIP	1000<	U/L
Cl	108	meq/L	CRP	15.2	mg/dL

Case study (4): Ultrasound test results in Case A — Fig. 12

- Acute vomiting and lethargy for 2 days

Case A



- Inflammation
- Low calcium
- Lipase & CRP elevation
- AUS

→ Dx. Acute pancreatitis AKI secondary to AP

Enlarged & Irregular hypoechoic pancreas
Hyperechoic mesentery & little fluids around pancreas

Case study (4): Blood chemistry test and urinalysis results in Case B — Fig. 13

- Acute vomiting and lethargy for 2 days

Case B

BUN	98	mg/dL
CRE	3.1	mg/dL
P	5.5	mg/dL
Ca	13.2	mg/dL
TP	8.1	g/dL
ALB	4.3	g/dL
GLB	3.8	g/dL
T-cho	185	mg/dL
Na	130	meq/L
K	5.8	meq/L
Cl	101	meq/L

USG	1.032

- Hypovolemia
- Low Na/K = 22.4
- Hypercalcemia
- ACTH-stim → cortisol < 1.0μg/dL

→ Dx. Hypoadrenocorticism Hypovolemic AKI

Case study (5): 10 years old, spayed female, mixed breed dog

Progress: loss of appetite over the past month, decreased activity, intermittent vomiting
Physical examination: normal TPR, BCS 4/9, mildly decreased muscle mass, 5% dehydration

Blood test results:

	Case		Ref range
Ht	32	%	37~55
Neu	16.0	x10³/μL	3~1.15
Lym	0.5	x10³/μL	1~4.8
Ret	158	x10³/μL	~100
PLT	230	x10³/μL	200~500
TP	5.3	g/dL	5.0~7.2
ALB	2.7	g/dL	2.6~4.0
GLB	2.5	g/dL	1.6~3.7
GLU	102	mg/dL	75~128

	Case		Ref range
BUN	101	mg/dL	9.2~29.2
CRE	1.8	mg/dL	0.4~1.4
T-BIL	0.1	mg/dL	0.1~0.5
ALT	72	U/L	17~78
ALP	82	U/L	~89
Ca	10.4	mg/dL	9.3~12.1
P	5.8	mg/dL	1.9~5.0
Na	142	mEq/L	141~152
K	3.5	mEq/L	3.8~5.0
Cl	110	mEq/L	102~117

Urinalysis: USG 1.045, no other abnormalities
Interpretation of blood test and urinalysis results: Abnormal values are shown in red; CBC showed mild anemia, with increased neutrophil count and lymphopenia which indicated the possibility of a stress leukogram. The reticulocyte count was also increased, suggesting regenerative anemia. Blood chemistry test results showed a severely elevated BUN level and mildly elevated CRE level, with no significant changes other than mild hyperphosphatemia. BUN/CRE ratio was 56, where the normal range is 10~20, BUN/CRE was significantly elevated. Differentiation of an elevated BUN/CRE ratio includes gastrointestinal bleeding, dietary influences such as high protein diet or postprandial, dehydration, and decreased muscle mass. Urinalysis showed concentrated urine, so renal intrinsic damage was unlikely. In addition, CBC showed regenerative anemia, and hemorrhage and hemolysis might be considered in the differential of it, but there were no other obvious hemolytic findings on blood chemistry test results and no obvious bleeding spots except in the gastrointestinal tract. Therefore, the possibility of dehydration or gastrointestinal hemorrhage was considered in the differential of azotemia with elevated BUN/CRE ratio in this case, and abdominal ultrasonography revealed severe thickening of the stomach wall, which led to the diagnosis of gastric adenocarcinoma by gastrointestinal endoscopy and biopsy. As azotemia can be caused by diseases other than kidney disease, it is necessary to comprehensively evaluate and interpret azotemia by combining not only blood chemistry tests but also urinalysis and imaging examinations.

Conclusion

Liver enzymes and kidney markers in blood chemistry tests can be elevated for a variety of reasons other than liver or kidney disease. Therefore, when evaluating the liver and kidneys, it is important not to use single parameters such as ALT or CRE, but to combine a comprehensive blood chemistry panel with urinalysis and imaging examinations to properly evaluate and identify the cause of the disease.

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FUJIFILM Corporation
26-30, NISHIAZABU 2-CHOME, MINATO-KU, TOKYO 106-8620, JAPAN