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Case report: Five year old rabbit that suffers from chronic hypoalbuminemia and hyperglycemia

Valerie Nagy and Esther van Praag

Lucky is a male gray spotted lop that has a complete butterfly coloring around his nasal region and relatively colored fur. He was neutered at young age. He started to suffer from problems with his eyes and lacrimal duct, prior to developing metabolic problems.

Lucky is a mini lop rabbit that was purchased from a pet store (Figure 1). He was born in August 2008 and castrated a few months later. As an adult, he weighs about 3.5 kg (7.7 lbs.) (Figure 2). Lucky is a nervous rabbit that reacts strongly to stress: shaking and fast breathing. This is especially the case when his cage is cleaned, when brushed and during the treatment of his runny eyes. Apart from this nervousness, Lucky is a healthy rabbit during the first years of his life, with the exception of stasis problems of the digestive system once a year. He lives in a big cage, but is free to

Figure 1: Lucky, a spotted lop rabbit suffering from several health problems, here in company of his partner Hunny.

Figure 2: Lucky is overweight in June and remains so a year later, in 2014, in spite of a strict and healthy diet.

run outside for a minimum of 8 hours per day. Despite a healthy diet, Lucky gained weight until the age of 6, after which he suddenly lost 0.5 kg (1.1 lbs.) and weighed 2.75 kg (6 lbs.) towards the end of his life, at the age of 7 (Figure 3). This loss of weight is accompanied by a decrease in appetite and a decrease in the size of solid fecal droppings. His coat in his face became rough looking because of the cleaning twice a day. The rest of his coat was smooth.

Ear Infection

Chronic otitis is more common in lop rabbits, as proper aeration of the outer ear canal is hindered by the falling ears. A surgical option is the widening of the entrance of outer ear canal, but results have not been as good as hoped in many rabbits.

Lucky suffered from a chronic infection of the external portion of the ear canal. The culture of a sample showed the massive

Figure 3: Lucky after losing weight.

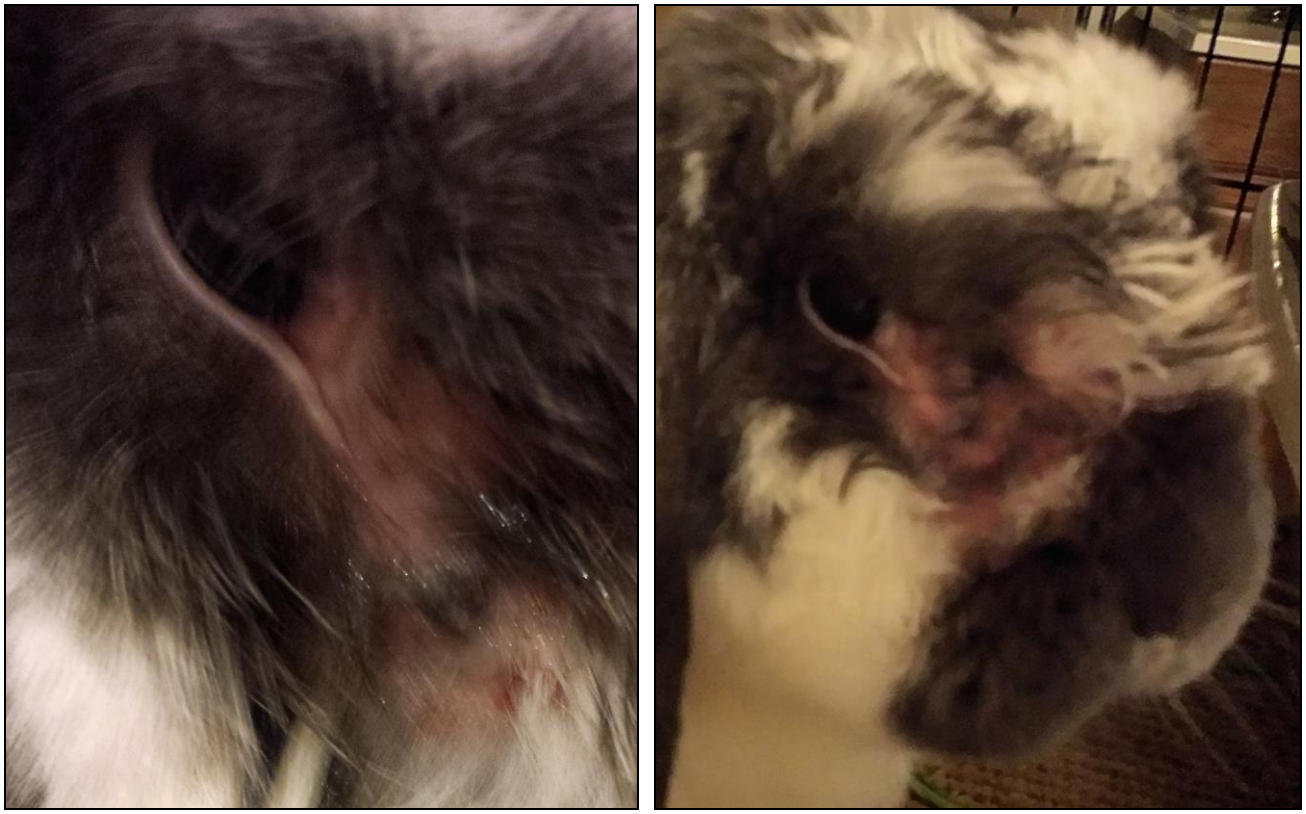

Figure 4: Irritation of the skin around the inner canthus of the eye, caused by a chronic lacrimation refractory to any attempted treatment with antibiotics or flushing.

presence of bacteria (+++) and, to a lesser extent, yeast (++). This condition was treated with a suspension of gentamycin, and Tris-EDTA, and penicillin injections every third day.

The infection was successfully treated.

Respiratory problems

Lucky suffered from an infection of the upper respiratory system. The culture of a nasal sample revealed the presence of coagulase negative staphylococcus.

Lacrimal duct and icterus

Lucky begins to suffer from persistent watery eyes (epiphora) and the presence of a thick mucus or white-colored discharge in the right eye, following by the left eye later at the age of 2 (Figure 4). It seems to be related to an infection of the nasolacrimal duct. The cause is unknown. It may relate to a slight bone deformation that compressed the duct, a scar from a traumatic event, or it may be congenital. X-rays did not reveal the presence of a skull anomaly, bone loss or dental disease.

Excoriation of the skin with inflammation of the dermis is observed around the internal cantus of the right eye (Figure 4). The lacrimal duct of each eye is flushed at regular intervals, without success.

Numerous antibiotic treatments are administered and attempts to irrigate the nasolacrimal canal have all remained without success.

An ulcerous lesion with the formation of scar tissue was present on the surface of the cornea. It was accompanied by a neovascularization in the white sclera of the eye, which, therefore, had a reddish

coloration. Lucky also suffered from injected sclera, meaning that blood has accumulated in the white part of the eye. Injected sclera can be caused by a chronic high level of glucose, a problem Lucky suffered from all his life.

Later in his life, the sclera of the eye took an off-white/yellowish coloration (icterus). It is usually caused by an accumulation of bilirubin. Bilirubin is a red-yellow pigment in urine and blood and bile, and results also from the degradation of hemoglobin in red blood cells. The blood test shows that bilirubin in his blood is normal, but this is not conclusive.

Itchy burning skin

Disorders of the thyroid gland can induce an itchy skin. In humans, patients suffering from thyroid disorders mention a feeling of tightness in the throat as well as pain and tenderness on the front of the neck and/or thyroid area.

With Lucky, he started to pull fur out of one spot on his chest directly below his neck. It seemed like an obsession or something was bothering him (Figure 5). Could he have experienced these side-effects of thyroid disease too ? His blood panel indicates dysfunction of this gland at the end of his life.

Echography and medical imaging

At the age of 4 years, x-rays of the skull were taken (Figure 6). They do not show abnormalities in the skeleton such as a decrease in bone density or dental problems that may lead to compression of the nasolacrymal duct.

At the age of 6, an ultrasound of the thorax was performed to exclude any problems in the chest and of the heart

Figure 5: Lucky would pull fur out of one spot on his chest directly below his neck. It seemed like an obsession or something was bothering him. Right: detail of the fur pulling in his neck.

before a small surgical procedure. No anomalies were observed.

An important blood component: albumin

Albumin is one of the three protein components present in the blood and also the main one (60%). The other two are globulins and fibrinogen. Albumin is a protein that is very soluble in water. It plays an essential role in the proper functioning of the body and is a marker of the general nutritional status. It also promotes the transfer of nutrients and wastes to and from the blood and cells. It plays further important roles, including:

- Transport of hormones, e.g. the active T_3 form of the thyroid hormone.
- Transport of endogenous substances, e.g. divalent cations (Ca, Zn). The binding of albumin with sodium ions Na^+ enables to attract fluids into the blood vessels. The binding of albumin with free radicals, free fatty acids, bilirubin or bacterial toxins reduces the toxicity of these molecules.

Figure 6: Lateral R and L and dorso-ventral x-rays of Lucky's skull. No anomalies or loss of bone density were observed.

- Transport of drugs via the blood circulatory system throughout the body.
- Transport of exogenous substances such as drugs, e.g. antibiotics (penicillin's cephalosporin's, sulfonamides, tetracyclines), anti-inflammatory analgesics (salicylic acid, ibuprofen), sedatives (phenobarbital, diazepam), certain drugs for cardiac, renal or nervous system problems, and diuretics.
- Neutralization of free radicals and toxins.
- Activation of blood platelets and transport of coagulation factors.
- Maintenance of the oncotic pressure within blood vessels.
- Maintenance of the fluid balance between the blood and the blood vessels and the interstitial fluid present between the blood capillaries and the cells.
- Maintenance of fluids in the blood vessels or passage of fluids from the blood to the tissue cells by regulating the speed and volume of exchanged fluids.

Moreover, the degradation of the albumin in inflamed tissues will supply them with the necessary amino acids, fatty acids and the zinc for their healing.

Endogenous albumin is produced in the liver only. Its production depends on a supply of nutrients and nitrogen from the diet. In humans, a nutritional intake is also possible with milk or eggs. While hepatocyte cells bordering the blood vessels free the synthesized albumin directly into the bloodstream, most of the albumin is transported by transcytosis.

The production of albumin in the liver is regulated according to the needs in the body. Synthesis of this molecule in hepatic cells is stimulated by a low level of albumin in the blood and by the hormones like cortisol (cortex of the adrenal gland), thyroxine (thyroid), and by growth hormones. The presence of toxic molecules in the liver, potassium and stress also influence the production of albumin. The production of albumin in the liver is inhibited when:

- The liver is not working properly,
- The diet is deficient in amino acids,
- The intestine badly absorbs proteins and/or amino-acids.
- Renal function is insufficient.

In such cases, administration of albumin may be considered.

A low level of albumin (hypoalbuminemia) in the blood is often associated to protein malnutrition or high glucose/diabetes, among others. In the case of protein malnutrition, the pancreas may fail to produce enough enzymes that will degrade protein in the intestine. If proteins are not degraded, the intestine will fail to absorb them into the blood circulation. Hypoalbuminemia leads to a deficient transport of substances, including drugs. In a healthy being, bilirubin, which is produced by the degradation of hemoglobin, will bind to albumin and be transported to the liver to be detoxified. When this is not possible, bilirubin becomes toxic. Bilirubin also competes with therapeutic molecules in the blood. If the latter no longer binds to albumin and circulates freely in the blood, side effects or even toxic effects may appear.

A high level of albumin in the blood is rare. It occurs in case of dehydration or is linked to the presence of a high level of thyroid hormone in the blood.

Reference values of serum proteins in a healthy rabbit:

- Albumin: 25-40 g/l
- Globulin: 1.5-3.3 g/dl or 25-40 g/l
- Albumin-globulin ratio: 0.7-1.89
- Protein – total: 50-75 g/l
- Bilirubin- total: 3.4-8.5 μmol/l or 0-0.75 μg/dl.
- Plasma: 44-71 g/l.

Analysis of the blood tests results

4 years old (August 2012)

A blood panels shows a few values that are off.

CBC: Slightly elevated hemoglobin
Low heterophils (neutrophils)

The slightly elevated hemoglobin is unlikely to be related to any condition of concern or it may be linked to the respiratory disease of Lucky.

Low heterophils are typically observed in cases of vitamin deficiency, of infection or autoimmune disease, of myelodysplastic or bone marrow disease, or splenomegaly.

Blood enzymes: ALT: normal (54 U/L)
ALP: elevated (78 U/L)

Healthy values are:
Alanine transaminase (ALT): 25-65 U/l
Alkaline phosphatase (ALP): 10- 70 U/l
Aspartate aminotransferase (AST): 10- 98 U/l

Chemistry: Phosphorus: low (3.7mg/dL)
Calcium: normal (15.1 mg/dL)
Glucose: elevated (256 mg/dL)

A low phosphorus level is observed in case of vitamin D deficiency, in malnutrition, hypercalcemia (calcium level is normal here) or an overactive parathyroid gland.

A high level of serum glucose in rabbits is often caused by the stress of manipulation during the physical examination by the vet. Lucky is overweight in spite of a healthy diet. He shows a chronic elevated level of glucose in all the blood tests, which hints to a more severe problem: a diabetes type of problem.

4 years and 10 months old (June 2013)

REMARK: the white of Lucky's eyes is slightly yellowish colored.

A new blood panels is done.

CBC: slightly low hemoglobin

Blood enzymes: ALT: normal (54 U/L)
ALP: normal (37 U/L)
AMY: normal (115 U/L)

ALT and ALP indicate a normal liver function.

Amylase (200-500 U/l) reflects the pancreatic activity. No blockage or inflammation, which leads to an increased level of this enzyme. It is normal. With normal pancreas and liver values, could Lucky suffer from a problem with his gallbladder ?

Chemistry: Albumin: low (2.0 g/dL)
Globulin: high (5.0 g/dL)
ALB/Glob = 0.4 (low)
Glucose: high (369 mg/dL)
BUN: normal (15 mg/dL)
Creatinine: normal (1.4 mg/dL)

Albumin is a marker of the general nutritional status and is usually associated to protein malnutrition, hypothyroidism, and/or a high level of glucose/diabetes, among others. In the case of protein malnutrition, the pancreas may fail to produce enough enzymes that will degrade protein into amino-acids in the intestine. It may also hint to an intestinal malfunction, with an inability to absorb proteins and amino-acids into the blood circulation.

An elevated level of globulins is usually associated to a chronic inflammatory disease. It may be the chronic ear infection, but may also hint an inflammatory problem in the intestine.

Glucose is high.

Kidney parameters are normal.

5 years and 9 months old (May 2014)

Many parameters are suddenly off.

CBC: Low heterophils (neutrophils)
High monocytes
High eosinophils

Heterophils (also called neutrophils in rabbits) are low, usually the sign of an infection or a nutrient/vitamin deficiency in rabbits.

Monocytes are high, usually a sign of chronic inflammation, possibly of fungal origin, the presence of parasites or a problem of the gastrointestinal system.

Eosinophils are high, possibly the presence of parasites, a skin issue or a gallbladder inflammation.

Blood enzymes: ALT: elevated (78 U/L)
ALP: elevated (75 U/L)
AST: normal (27 U/L)

AST is normal, while ALT and ALK are elevated.

Elevated ALK and ALT only is typically observed in case of bile duct, or gallbladder dysfunction. If the blockage is partial, there is often no rise in bilirubin in the blood serum. The blockage can be caused by a mass (cancer or benign) or stones.

(Fatty liver is ruled out; this condition is accompanied by normal values for AST and ALT).

A failure of the gallbladder and an impaired bile flow will affect the pancreas and intestine.

Chemistry: Albumin: high (5.1 g/dL)
Globulin: high (2.7 g/dL)
ALB/Glob = 1.8
Phosphorus: low (3.3 mg/dL)
Glucose: high (348 mg/dL)
Calcium: high (17.1 mg/dL)
Sodium: high (182 Eq/dL)
Chloride: high (129 Eq/dL)
BUN: normal (24 mg/dL)
Creatinine: normal (1.2 mg/dL)

Albumin is suddenly high, an indicator of dehydration mainly, while globulins are low. The latter is often indicative of inflammatory bowel disease. As for low proteins, it may also indicate protein malnutrition

The level of several serum electrolytes are off, indicating dehydration or a dysfunction of the thyroid or the parathyroid gland.

Analysis of the blood panel results

The low levels of albumin during the last years of Lucky's life tend to indicate that he suffered from chronic protein malnutrition. A congenital intestinal problem with poor absorption of proteins and amino acids or a failure to produce enough proteins degrading enzymes by the pancreas ?

Or both ?

Lucky is a spotted rabbit, though rather colored and with a complete butterfly around his nasal region. These rabbits usually do not suffer from megacolon. Yet, the raised level of globulins may hint a chronic intestinal inflammation. Could it be a form of megacolon leading to nutrient deficiencies ?

The failure to degrade protein properly by pancreas enzymes leads to poor absorption of amino-acids in the intestine. The amino-acids methionine and cysteine in particular are needed to form insulin in the pancreas. When these amino acids are low, insulin production will be low. This may explain the chronic high levels of glucose observed in the Lucky's blood.

Protein malnutrition is associated to a change in fur in rabbits: sparse and loss of its normal sleek and shiny appearance (Figure 7).

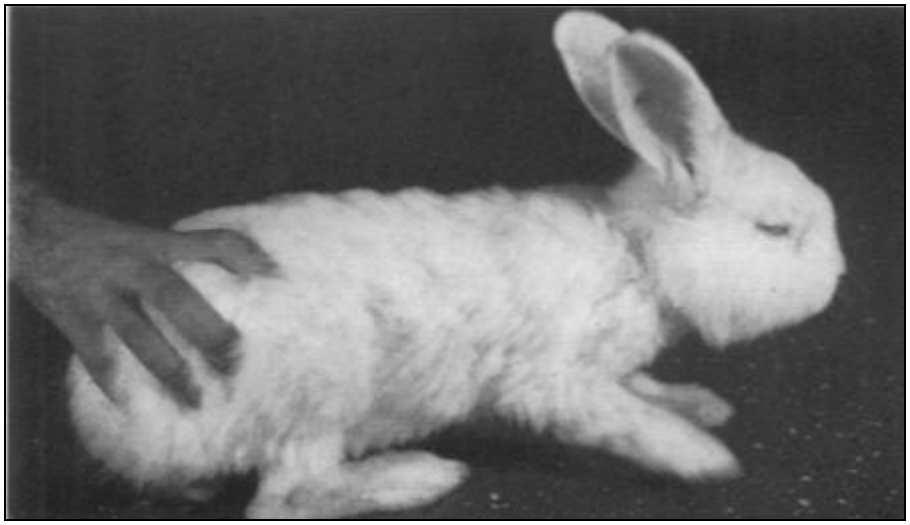

Figure 7: A rabbit on deficient diet for 14 weeks. The animal is markedly undersized. The fur is somewhat sparse and has lost its normal sleek and shiny appearance. Reprinted from: Volk BW, Lazarus SS. Am J Pathol. 1960;37(2):121-35.

Gastrointestinal malabsorption of nutrients may also be the result of an overactive thyroid or parathyroid gland. The latter is associated to nervousness. Although Lucky has always been a nervous rabbit, it does not allow to conclude that he suffered from hyperthyroidism in the early years of his life already. It is only at the end of his life that abnormal serum electrolyte values hint to parathyroid gland hyperactivity. The cause of this hyperactivity is unknown.

The liver parameters (normal AST, elevated ALT and ALK) are indicative of a gall bladder dysfunction, e.g. a blockage or the presence of gallbladder stones. This was accompanied by the somewhat yellowish coloring of the sclera in his eyes. Both gallbladder and parathyroid gland may be associated. Indeed the parathyroid gland is involved in the calcium metabolism. When this gland is hyperactive, the level of calcium in the blood increases. An increased level of calcium in the blood may lead to the formation of gallstones in the gallbladder. The icterus in his eyes tends to indicate that the gall-bladder blockage may have been present already before the elevation of serum calcium.

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