



Gastroenteropathy in Norwegian Lundehunds

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ABSTRACT: Norwegian Lundehunds are often affected by gastrointestinal disease, the most common clinical signs of which are intermittent diarrhea, vomiting, weight loss, lethargy, ascites, and subcutaneous edema of the hind legs. The most frequent laboratory changes include hypoalbuminemia (with or without hypoglobulinemia), hypocalcemia, a decrease in the serum cobalamin concentration, and an increase or decrease in the serum folate concentration, reflecting microbial synthesis or malabsorption, respectively. Histopathologic abnormalities can include chronic atrophic gastritis, intestinal lymphangiectasia, and lymphoplasmacytic enteritis. Because the underlying cause of gastroenteropathy in Norwegian Lundehunds has not been identified, treatment is symptomatic.

The Norwegian Lundehund (“puffin dog”) is a small, 14- to 20-lb (6- to 9-kg) spitz-type canine breed originating from northern Norway, Iceland, the Faroe Islands, the Orkney Islands, and the Hebrides¹ (Figure 1). One of the breed characteristics is polydactyly (Figure 2); in fact, the breed standard of the Norwegian Kennel Club requires that Norwegian Lundehunds have at least six toes on each foot.^a In addition, their joints are unusually flexible, making it possible for these dogs to stretch out their front legs laterally and bend

their necks far backwards (Figure 3). Lundehunds can also retract the cartilage of their ears to voluntarily close their ear canals.² The Norwegian Lundehund is an old breed, dating back to the 17th century.³ The breed was thought to be extinct until a surviving population was discovered in 1925 on the island of Væroy, Norway.³ After almost all of the population was lost as a result of distemper and other circumstances, a breeding program was started in 1961 with only five remaining dogs, consisting of two females and three males.⁴ In 1964, one of the original males developed ascites, edema of the hind legs, and gastrointestinal (GI) disturbances at 3 years of age.¹ Since then, several authors have reported a

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^aNorsk Kennel Klub, FCI standard 265.



Figure 1. A typical Norwegian Lundehund.



Figure 2. Polydactyl foot of a Norwegian Lundehund. Note the desired double dewclaws.

Figure 3. Norwegian Lundehunds have extremely flexible shoulder joints and necks.



similar clinical presentation, called *Lundehund syndrome*, in Norwegian Lundehunds in Europe and North America.^{1,5-7} It is assumed that the prevalence of this gastroenteropathy in Norwegian Lundehunds in the United States is high, although accurate estimates of the prevalence in the United States or elsewhere have not been established.⁵

CLINICAL, GROSS PATHOLOGIC, AND HISTOPATHOLOGIC FINDINGS

Norwegian Lundehunds affected by gastroenteropathy may exhibit a variety of clinical signs, including intermittent diarrhea, vomiting, weight loss, lethargy, ascites, and subcutaneous edema, mostly of the hind legs.^{1,4,5} However, there is evidence that subclinical disease is also very common.

In the past, this disease has been referred to merely as *protein-losing enteropathy* (PLE), although it is now well established that gastric abnormalities are present as well.^{1,4,5,8} Lundehund syndrome, as described in this article, may include components of gastritis, PLE, intestinal lymphangiectasia, inflammatory bowel disease (IBD), and malabsorption and has been described in the Lundehund populations of Europe and North America.^{1,4-7}

Most studies evaluated only a small number of dogs; therefore, care should be taken in extrapolating findings to the whole breed. However, many findings seem to be consistent throughout the different reports, indicating that they are probably widespread abnormalities within the existing population of Norwegian Lundehunds worldwide.

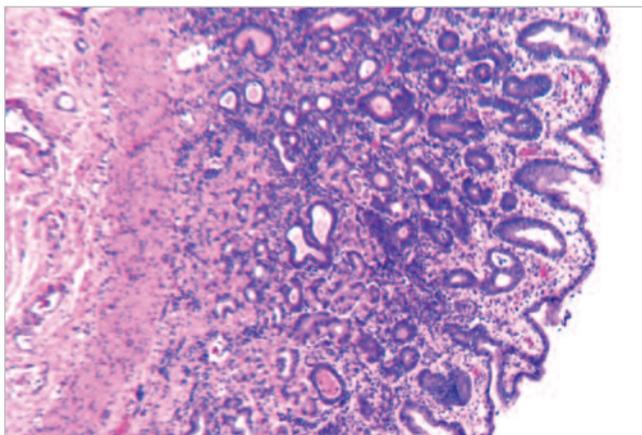


Figure 4. Histopathologic image of the gastric mucosa in a dog with Lundehund gastroenteropathy. Note the mononuclear cell infiltrate. (Hematoxylin–eosin; original magnification $\times 100$).

PATHOLOGY AND HISTOPATHOLOGY

Some Norwegian Lundehunds never exhibit signs of GI disease. However, investigations have shown that even Lundehunds that appear healthy often have abnormal histopathologic findings within the GI tract. These abnormalities can be seen throughout the stomach and small intestine, with the severity of the changes generally decreasing from the proximal to the distal

tinal lymphangiectasia. Macroscopic findings in the stomachs of Lundehunds included submucosal edema, mucosal erosion, and thickening of the stomach wall due to formation of firm, fibrous, grayish-white tissue.⁴ The major histologic finding was the presence of gastritis in all 14 Lundehunds studied. The changes were mainly localized to the gastric fundus and body and were identified as chronic atrophic gastritis in most Lundehunds, based on observation of degenerated fundic glands and mononuclear cell infiltration (Figure 4). In some Lundehunds, dilated gastric lymphatics were observed. Histopathology revealed the presence of primary gastric carcinoma in four dogs. Gastric granulomas, consisting of epithelioid-like cells with a center of fibrous material, were found in six Lundehunds, mainly in the submucosa of the pyloric antrum.⁴ However, intestinal metaplasia, a premalignant condition described in humans resulting from atrophic gastritis and characterized by the presence of enterocyte-like cells with a brush border and goblet cells, was not found in the Lundehunds.^{4,8–10}

These results suggest a possible link between the occurrence of intestinal lymphangiectasia and chronic atrophic gastritis or even gastric carcinoma in Lundehunds and that Lundehunds with chronic atrophic gastritis may have an increased risk of developing gastric

All Norwegian Lundehunds should be monitored frequently for hypoproteinemia and fecal protein loss to facilitate early symptomatic treatment and exclude severely affected dogs from breeding.

intestinal tract.^{1,6} To obtain reliable results, intestinal biopsy specimens should be obtained from live dogs or within 5 minutes of euthanasia to avoid subtle post-mortem changes that can be confused with changes characteristic of Norwegian Lundehund enteropathy.⁶

At necropsy, various degrees of emaciation have been observed in Norwegian Lundehunds.¹ In severe cases, ascites is common and often accompanied by hydrothorax, hydropericardium, and subcutaneous edema. Analysis of the ascites fluid has revealed no or little protein and a specific gravity below 1.018, which is a classic feature of pure transudate.¹

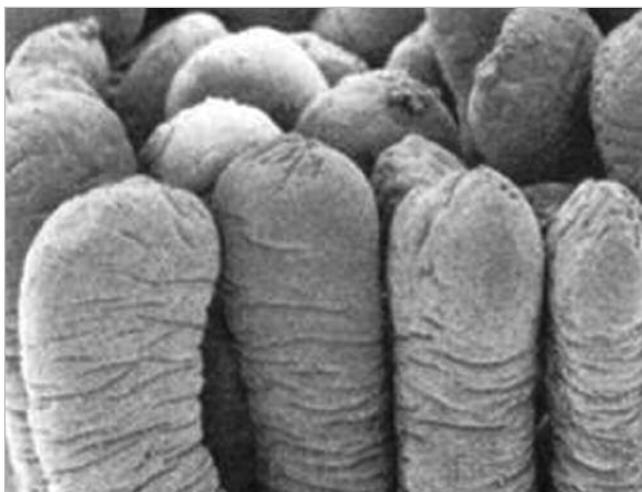
Stomach

Kolbjørnsen et al⁴ reported gastric abnormalities during necropsy of 14 Lundehunds diagnosed with intes-

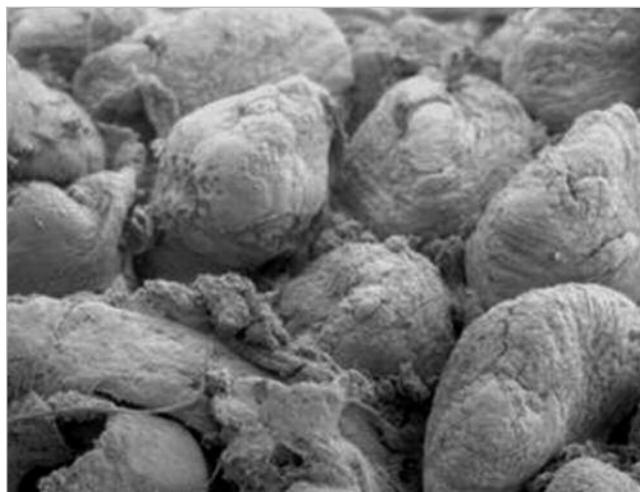
tinoma. It has been shown that chronic atrophic gastritis is a predisposing condition for the development of gastric carcinoma in humans, often following or concurrent with *Helicobacter pylori* infection.^{9,10} Spiral bacteria (i.e., *Helicobacter* spp) were not detected in any of the Lundehunds examined.⁴

Small Intestine

Morphologic changes of the intestines of Norwegian Lundehunds have been described in several reports. Frequent macroscopic findings during necropsy included whitish, dilated mesenteric and subserosal intestinal lymphatic vessels. The mucosa of the small intestine appeared thickened and rough or granular.^{1,5,6} The villi appeared whitish and enlarged, with a patchy or diffuse pattern of distribution.^{1,6}

Figure 5. Images from a scanning electron microscope.

Normal ileal mucosal surface.



Villus atrophy in the ileum of a Norwegian Lundehund.

Histologic examination revealed thickening of the mucosa in the duodenum and jejunum, villus atrophy (Figure 5), and villus fusion.^{1,6} Crypt hyperplasia and filling of the crypts of Lieberkühn with mucin and cellular debris were also observed.⁶ The epithelium appeared attenuated with a thinned brush border, was frequently desquamated from the lamina propria due to subepithelial fluid accumulation, and was often associated with edema in the lamina propria.^{1,6} Lymphoplasmacytic infiltration was also found, indicating the presence of an inflammatory process^{1,5} (Figure 6).

Intestinal lymphangiectasia was frequently described.^{1,4-6} Lymphangiectasia was characterized by balloon-like distentions of villi and occasional villus rupture but was also present in deeper sections of the intestinal wall, with lacteals protruding toward the serosal and mesenteric surface in some cases^{1,6} (Figure 7). Granulomas associated with lymphatic vessels have been observed.⁵ Granulomatous changes are often found in the small intestinal mesentery of dogs with intestinal lymphangiectasia and are thought to be a result of leakage of lymph into the surrounding tissue.¹¹⁻¹⁵ Lymphangiectasia in Norwegian Lundehunds has similarities to primary lymphangiectasia in humans.⁶ Primary intestinal lymphangiectasia is a congenital defect within the lymphatic system characterized by hypoplasia of lymphatic vessels, which creates a functional obstruction to lymphatic flow and subsequently leads to dilation of lymph vessels throughout the body.¹⁶ It has been speculated that the underlying defect may be an inability of the lymphatic system to form effective anastomoses to

bypass the lymphatic obstruction.⁶ This disorder would subsequently lead to increasing pressure within the lymph vessels, causing them to dilate and possibly rupture. In contrast, secondary lymphangiectasia is caused by obstruction of lymph vessels due to neoplasia, inflammation, or elevated venous pressure.^{6,17} No evidence of secondary lymphangiectasia has been reported in Lundehunds; thus, it is assumed that lymphangiectasia in this breed is primary, although it should be remembered that intestinal inflammation, as described in Lundehunds, could also contribute to lymphangiectasia, especially if there is a genetic predisposition to the development of primary lymphangiectasia.

Pancreas

Abnormalities in the pancreas of Norwegian Lundehunds were reported in one study.¹ During macroscopic examination, the pancreas was often edematous, and small areas of peripancreatic fat necrosis were found in some cases. Acute pancreatitis was diagnosed in one dog, although it is unknown how this diagnosis was made, and histopathologic alterations in this patient were not detailed. During histopathologic examination, dilated interstitial lymph vessels were found in the pancreas.¹ None of the other studies describes any pancreatic abnormalities in the dogs examined, so the significance of this single study is unclear.

Implications for Prevalence of Disease

It is remarkable that all of the Lundehunds that were examined by histopathology were affected by at least

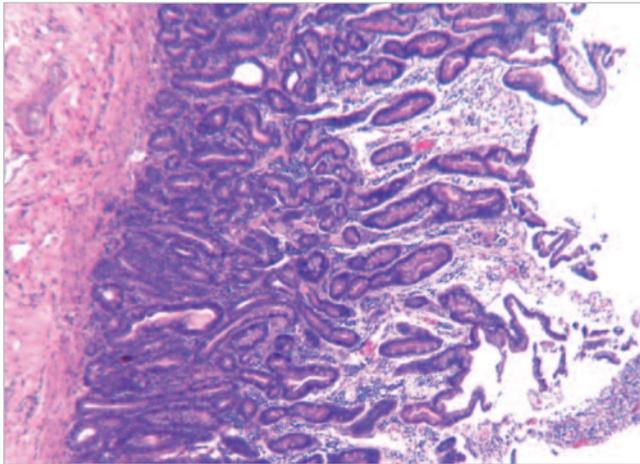


Figure 6. Lymphocytic–plasmacytic enteritis in a Lundehund. (Hematoxylin–eosin; original magnification $\times 100$)

some of the abnormalities mentioned above and none was free of GI abnormalities. This suggests that the actual prevalence of gastroenteropathy within this breed is very high and that many Lundehunds that seem healthy may, in fact, be affected by gastroenteropathy.

DIAGNOSIS

Signalment and Clinical Signs During Examination

Of 43 Lundehunds that were examined in different studies, information about the sex and age was available for 36 dogs. Fifteen of 36 dogs (41.7%) were female, and 21 (58.3%) were male. The mean age for the 36 dogs was 5.2 years (range: 0.5 to 10 years).^{1,4,6,7}

The clinical signs observed in the 43 Lundehunds included diarrhea (76.7%), vomiting (72.1%), ascites (46.5%), edema (44.2%), weight loss (32.6%), and lethargy (20.9%). Most of the dogs presented with several of these clinical signs at the same time, and the most common combination was diarrhea with vomiting and ascites and/or edema. One of the 43 dogs was apparently clinically healthy. The clinical history was unavailable for one dog.^{1,4-7}

Clinical Pathology

Hematology

Hematologic examinations, including hematocrit, erythrocyte sedimentation rate, erythrocyte counts, and leukocyte differential counts, were conducted in three investigations, and no abnormalities were reported in any of these studies.^{1,4,5} Lymphopenia has been fre-

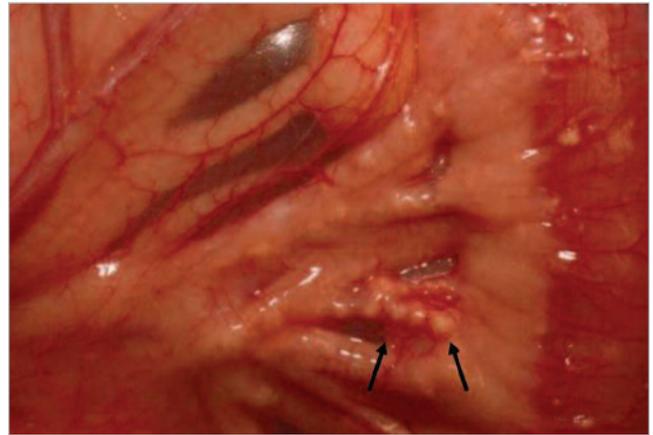


Figure 7. Intestinal lymphangiectasia in the jejunal mesenteric surface of a Norwegian Lundehund. The arrows show granulomatous changes associated with lymphangiectasia.

quently reported in dogs of other breeds with PLE, but this did not appear to be the case in the Lundehunds examined. The reason for the absence of lymphopenia is unknown.

Serum Biochemistry Profile

The following serum parameters have been investigated in different studies: serum total protein, albumin and globulin, calcium, phosphorus, magnesium, cholesterol, urea nitrogen, aspartate transaminase, alanine transaminase, and alkaline phosphatase. The results for most serum parameters were within the reference range, with the exception of the serum total protein, albumin, and calcium concentrations.^{1,5}

Hypocholesteremia is often found in patients with PLE due to a lack of fat absorption, but this was not reported in the studies investigating Lundehunds. However, the cholesterol level was measured in only a small number of patients ($n = 11$) and, therefore, may not be fully representative of the affected population. It is also interesting that the serum magnesium concentration was normal in all the Lundehunds tested, although this parameter was also determined in only a very small number of dogs ($n = 5$). Hypomagnesemia can develop as a result of chronic diarrhea and malabsorption due to various intestinal mucosal diseases, including intestinal lymphangiectasia.¹⁸⁻²⁰ Possible mechanisms leading to malabsorption of magnesium are reduced mucosal surface area, increased intestinal secretion, vitamin D deficiency, and formation of insoluble magnesium soaps with unabsorbed fat.¹⁸ Dogs

with small intestinal inflammation can have mildly increased liver enzyme concentrations due to development of a “reactive hepatopathy,” but this was not observed in the Lundehunds investigated.²¹ Further studies are needed to determine whether these findings are representative of Lundehund gastroenteropathy or were falsely negative due to the low number of dogs evaluated so far.

Clinicians should pay close attention to the coagulation profile because these patients may develop thromboembolic disease. The major mechanism seems to be loss of antithrombin III concurrent with intestinal loss of other plasma proteins, inducing a hypercoagulable state.^{17,20} Up to 10% of all dogs with PLE are affected by this complication, but the incidence of a hypercoagulable state in Norwegian Lundehunds is unknown.²² Also, intestinal fat malabsorption can reduce the absorption of the fat-soluble vitamin K, which may lead to vitamin K deficiency and increase the risk of bleeding in affected

trations in seven Lundehunds, six of which had a history of diarrhea and weight loss but were not necessarily exhibiting any clinical signs of disease during testing. One dog had no history of GI problems. Although these dogs did not appear to be sick, hypoalbuminemia was present in three of the seven dogs, whereas the serum globulin concentration was normal in all dogs tested.⁵

Thus, hypoalbuminemia could be identified in 21 of 26 dogs (80.8%), hypoglobulinemia in 13 of 26 dogs (50%), and general hypoproteinemia in 17 of 26 dogs (65.4%). In addition to these study results, Kolbjørnsen et al⁴ found hypoproteinemia in seven of 13 dogs for which clinical data were available, but it was not specified whether this included hypoalbuminemia only, hypoglobulinemia only, or panhypoproteinemia.

Because liver enzyme abnormalities were not identified in any of the studies, it is unlikely that hypoalbuminemia is caused by a decrease in hepatic albumin

While the gold standard for the diagnosis of gastroenteropathy in Lundehunds is histologic examination of GI biopsy samples, assessment of the GI health of a Lundehund can be facilitated by measurement of fecal α_1 -proteinase inhibitor and serum albumin, globulin, cobalamin, and folate concentrations.

patients. While none of the clinical studies has examined coagulation profiles in Lundehunds, Kolbjørnsen et al⁴ noted thrombosis of gastric submucosal vessels in two of 14 Lundehunds during necropsy. In addition, a thrombus in the pulmonary artery was found in another dog.⁶ These studies suggest that Lundehunds with gastroenteropathy are at risk of developing thromboembolic disease; therefore, a coagulation profile should be routinely evaluated.

Serum total protein and albumin concentrations—Two different studies investigated serum protein concentrations in a total of 19 Lundehunds affected by gastroenteropathy.^{1,7} All the dogs were hospitalized for clinical signs of disease when the samples were obtained. Fourteen dogs were hypoproteinemic, whereas four had hypoalbuminemia only. Five dogs were hypoglobulinemic.^{1,5,7} One dog had a normal serum albumin concentration and slightly elevated serum total protein and globulin concentrations.⁷ A preliminary study by Williams and Melgarejo⁵ investigated protein concen-

trations due to liver disease. Most dogs with PLE have decreased albumin and globulin concentrations.²¹ However, in some dogs, hypoalbuminemia is accompanied by normal globulin concentrations or hyperglobulinemia rather than hypoglobulinemia. This mostly occurs in Basenjis with immunoproliferative small intestinal disease, although it can occur in dogs with certain infectious diseases leading to globulin production, such as ehrlichiosis, histoplasmosis, heartworm disease, or chronic inflammatory liver disease.²¹⁻²³ It is not clear why some Lundehunds with PLE have normal globulin concentrations, but it could be hypothesized that this may simply reflect progression of the severity of the disease, with initial hypoalbuminemia as the only finding in less severely affected dogs and panhypoproteinemia in severely and often chronically affected dogs. We have recently evaluated serum total protein, albumin, and globulin concentrations in approximately 100 Norwegian Lundehunds. Hypoproteinemia based on serum total protein concentrations was found in more than

50% of dogs, hypoalbuminemia in approximately 40% of dogs, and hypoglobulinemia in approximately 15% of dogs. None of the dogs in our study presented with hyperglobulinemia.

The specific mechanism of enteric protein loss in Lundehunds is unknown. Rupture of lymphatic vessels due to intestinal lymphangiectasia, leading to loss of chylous protein, is likely a major cause. However, investigations have shown that increased mucosal tissue pressure, as occurs in edematous tissue, can cause passive secretion of tissue fluids and their components, including protein.²⁴ Intestinal inflammation could also contribute to protein loss. Therefore, a combination of several pathologic mechanisms leading to enteric protein loss in Lundehunds is likely.

Calcium concentrations—In two studies, serum total calcium concentrations were measured in five and three Lundehunds, respectively, and both found mild to moderate hypocalcemia in all dogs evaluated.^{1,7} Low serum calcium concentrations were attributed to hypoalbuminemia due to loss of protein-bound calcium. Because approximately 40% of serum calcium is bound to albumin, enteral loss of albumin in patients with PLE can cause a decrease in the serum total calcium concentration while increasing fecal calcium output.^{11,25-27} It has recently been shown that some dogs with GI diseases have low total and ionized serum calcium concentrations and remain hypocalcemic even after correction for the serum albumin concentration.^{17,19,20,27} Thus, it is apparently more accurate to measure the ionized fraction of serum calcium than the total serum calcium concentration. Unfortunately, these data are not available for Norwegian Lundehunds because only total calcium concentrations have been reported to date. The exact cause of this generalized hypocalcemia is unclear, but a variety of mechanisms other than hypoalbuminemia may contribute to hypocalcemia in dogs with GI disease. For example, malabsorption of dietary fats can reduce calcium absorption because unabsorbed fatty acids bind calcium and prevent calcium absorption.²⁶ Calcium absorption is also tightly regulated by the serum concentration of 1,25-dihydroxycholecalciferol, the active metabolite of vitamin D. Malabsorption of vitamin D, as may occur during small intestinal disease, could subsequently lead to vitamin D deficiency and, therefore, contribute to the development of hypocalcemia.²⁷

Intestinal Function Testing

Serum cobalamin and folate concentrations—Cobalamin is a water-soluble vitamin that undergoes a

complex series of biochemical reactions before being absorbed in the distal small intestine. Therefore, the serum cobalamin concentration is often decreased in patients with diseases involving the distal small intestine. Folate is also a water-soluble vitamin but is absorbed in the proximal small intestine; thus, a decrease in the serum folate concentration indicates involvement of that part of the small intestine. An increase in the serum folate concentration may indicate the presence of small intestinal bacterial overgrowth (SIBO) or some other shift in the upper small intestinal microflora. Both vitamins can be measured in serum using a commercial chemiluminescence immunoassay.

Cobalamin and folate concentrations were measured in a preliminary study in seven Lundehunds.⁵ The serum cobalamin concentration was subnormal (<225 ng/L) in three dogs, and the serum folate concentration was above normal (>17.4 µg/L) in two dogs.⁵ More recently, we measured cobalamin and folate concentrations in a large number of Lundehunds and found a decreased cobalamin concentration in approximately 10% of the dogs and a decreased serum folate concentration in approximately 13% of the dogs. An increased folate concentration was detected in approximately 40% of the dogs. The serum cobalamin assay appears to be helpful in assessing intestinal absorptive dysfunction in Norwegian Lundehunds, although not all dogs that are diagnosed with GI disease have a decreased cobalamin concentration. This is possibly due to the fact that a large number of Lundehund owners participate in a variety of research projects and are thus aware of the risk for cobalamin deficiency in their dogs and are regularly supplementing them. Therefore, the data accumulated may not reflect the actual prevalence of cobalamin deficiency in untreated dogs and should be evaluated with caution.

Several factors could lead to malabsorption of cobalamin in Lundehund gastroenteropathy. Chronic small intestinal inflammation can damage the specific receptors needed for absorption of cobalamin in the distal small intestine.^{28,29} Also, the stomach fulfills an important function in cobalamin absorption. While, in humans, a large portion of intrinsic factor is synthesized in the stomach, in dogs, this portion is likely less than 10%; thus, lack of intrinsic factor due to atrophic gastritis is unlikely a significant factor. However, another important component involved in cobalamin absorption is R protein, which is secreted by the gastric mucosa and, therefore, may be affected by atrophic gastritis. A lack of R protein could

disturb the complex mechanism of cobalamin absorption, thereby promoting cobalamin malabsorption.³⁰

The fecal α_1 -proteinase inhibitor ($F\alpha_1$ -PI) immunoassay—This assay is used to detect the presence of intestinal protein loss in patients with GI disease and suspected PLE. Historically, PLE has been assessed using ⁵¹chromium chloride (⁵¹CrCl₃), a radioactive isotope. ⁵¹CrCl₃ can be used to radiolabel albumin ex vivo, with subsequent intravenous administration of the labeled protein, or can be given intravenously, leading to in vivo radiolabeling of albumin. If the patient has PLE, the radioactivity from enterically lost ⁵¹CrCl₃ can be measured in the feces.^{31,32} Although this method is still considered the gold standard for PLE testing, it is impractical for clinical practice because the use of radioactive material is limited to certified institutions and the administration of ⁵¹CrCl₃ requires confinement of the dog in certified premises for several days after conducting the test. The fecal test to quantify $F\alpha_1$ -PI concentration is not invasive and avoids the need for handling and storage of radioactive waste. This test requires the owner of the dog to collect three separate fecal samples into special tubes (Figure 8), preferably from consecutive bowel movements, which need to be frozen immediately and, after the collection cycle has been completed, shipped frozen to the GI Laboratory at Texas A&M University (www.cvm.tamu.edu/gilab), which is currently the only laboratory offering this test. The reference range for $F\alpha_1$ -PI is 0 to 5.7 $\mu\text{g/g}$. Because of normal variation, healthy dogs can occasionally have a single elevated $F\alpha_1$ -PI concentration. If a single fecal sample has a concentration greater than 15 $\mu\text{g/g}$ or if the mean concentration of all three samples exceeds 9.4 $\mu\text{g/g}$, PLE is diagnosed. This method of interpretation reduces the probability of obtaining false-positive results.

Measurement of $F\alpha_1$ -PI in a small study with seven Lundehunds showed elevated concentrations (>6 $\mu\text{g/g}$ of feces) in five dogs, three of which also had hypoalbuminemia. The fecal excretion of intravenously administered ⁵¹CrCl₃ was increased in three of four dogs, which also had increased $F\alpha_1$ -PI concentrations, indicating a high prevalence of PLE in this breed.⁵

We have also obtained $F\alpha_1$ -PI results from approximately 100 Lundehunds in North America, more than 40% of which had mean $F\alpha_1$ -PI concentrations of 9.4 $\mu\text{g/g}$ or more, suggesting that PLE is common in Norwegian Lundehunds. It should be noted that the measurement of $F\alpha_1$ -PI is not indicated in every Lundehund. If a patient presents with chronic clinical



Figure 8. Collection of a fecal sample to measure the α_1 -proteinase inhibitor concentration. Approximately 1 g of feces has to be collected into special tubes.

signs of GI disease, has panhypoproteinemia, and has no hepatic or renal abnormalities, PLE can be diagnosed without the measurement of $F\alpha_1$ -PI. However, not all patients with PLE have signs of GI disease, and this test may be useful to screen these patients.

The xylose absorption test—This test has been conducted in Lundehunds with nonspecific GI signs.⁷ A xylose solution is administered by gastric gavage using a gastric tube. The concentration of xylose in plasma is then determined at half-hour intervals for 3 hours after the test solution has been given.⁷ Of the three dogs tested, only one had a marginally decreased xylose concentration (43.5 mg/dl after 1 hour).⁷

Pancreatic Function Testing

The serum canine trypsin-like immunoreactivity (cTLI) test—Measurement of trypsin and trypsinogen in serum can be used to diagnose exocrine pancreatic insufficiency (EPI), with a low cTLI concentration being strongly suggestive of EPI.^{28,33,34} When serum cTLI is normal, abnormal serum vitamin concentrations indicate the presence of small intestinal disease. In one study, serum cTLI concentrations were normal in all seven Lundehunds.⁵ In addition, we have recently evaluated cTLI concentrations in approximately 100 Lundehunds. Only one dog had a serum cTLI concentration diagnostic for EPI; three additional dogs had slightly subnormal serum cTLI concentrations. These findings suggest that EPI is uncommon in Norwegian Lundehunds and that decreased serum cobalamin and folate concentrations almost always reflect malabsorption due to small intestinal disease.

Hepatic Function Testing

The bromsulphophthalein (BSP) retention test—

This test was used to evaluate hepatic function in 11 Norwegian Lundehunds.¹ BSP is a cholephilic dye that is administered intravenously, undergoes hepatic uptake, and is excreted in bile. An increased retention of BSP 30 minutes after administration may indicate impaired hepatic function.^{35,36} Flesjå and Yri¹ found a 30-minute BSP retention of 30% in one Lundehund and less than 10% in the other 10 dogs, indicating normal liver function in all but one of the dogs. It was concluded that the high retention rate for the one dog may have been due to the fact that the dog had ascites, although the authors did not speculate as to the mechanism of this association.¹ Possible causes may be hepatic congestion, delayed cholephil circulation to the liver, diffusion of BSP into ascitic fluid, or even an overdose of BSP due to falsely increased body weight resulting from abdominal fluid accumulation.^{35,36} Although the test used has subsequently been shown to have poor sensitivity and specificity compared with serum bile acid and ammonia testing, these data suggest that Lundehunds generally have normal hepatic function.³⁵

Summary

One of the most dramatic changes apparent in Lundehund gastroenteropathy is protein loss, which can be severe in individual patients. Therefore, serum total protein, albumin, and globulin concentrations should be evaluated in Lundehunds presenting with clinical signs of small intestinal disease. If PLE is suspected, but serum protein concentrations are not grossly abnormal, the $F\alpha_1$ -PI test may be helpful in the diagnosis because the $F\alpha_1$ -PI concentration may be increased before the serum protein concentration becomes abnormal.²⁸ Another important parameter in assessing small intestinal disease in Lundehunds is the serum cobalamin concentration, which should ideally be evaluated in combination with the serum folate and cTLI concentrations. Potential deficiencies of other nutrients, including vitamins A, D, E, and K, should be considered.

Urinalysis

Urine parameters examined included color, odor, sediment, pH, specific weight, and the presence of blood as well as concentrations of protein, sugar, bilirubin, ketone bodies, and bacteria. Samples were examined in two studies, but no abnormalities were reported.^{1,5} This further confirms that hypoalbuminemia and hypoproteinemias in Norwegian Lundehunds are results of enteric rather than renal protein loss.

Fecal Sample Analysis

Several studies have investigated potential irregularities in Lundehund feces, which are often grossly mucoid or excessively liquid and have a sour or fetid smell in affected dogs.^{1,7} Bacteriologic and parasitologic examinations have not revealed any abnormalities.¹

Diagnostic Imaging

Findings from diagnostic imaging using radiography or ultrasonography are often nonspecific in dogs with GI disease, and it can be especially difficult to differentiate intestinal lymphangiectasia from other types of small intestinal disease.¹⁷ Nevertheless, ultrasonographic examination in patients with suspected intestinal disease can confirm the suspicion and facilitate initiation of further diagnostics, such as endoscopy and histopathology of biopsy specimens. Abdominal ultrasonography can show various degrees of intestinal wall thickening, hyperechogenicity of the small intestinal mucosa, loss of intestinal wall layering, and regional lymphadenopathy.^{17,37} In one study that evaluated ultrasonographic characteristics in 17 dogs (none of which was a Lundehund) with intestinal lymphangiectasia, ultrasonographic abnormalities did not seem to correlate with the severity of intestinal lymphangiectasia, and the small intestinal wall thickness observed during ultrasonography did not always correlate with the thickening of the small intestine seen during surgery in the dogs investigated.¹⁷ Another investigation found intestinal wall thickness and loss of wall layering to be significantly greater in dogs with intestinal neoplasia compared with dogs with intestinal inflammation.³⁷ Regional lymphadenopathy also seems to be more common and more severe in patients with intestinal neoplasia.^{37,38} None of the studies investigating intestinal disease in Norwegian Lundehunds has described diagnostic imaging. Therefore, it is unclear how Lundehund gastroenteropathy would manifest during abdominal radiography or ultrasonography. However, it is reasonable to assume that findings during these imaging studies would mirror those in dogs with similar GI disorders.

In summary, diagnostic imaging is useful in determining the presence of intestinal disease, and although findings can be very heterogeneous and do not always yield enough information to differentiate types of small intestinal disease, diagnostic imaging can be an indicator of whether neoplasia may be present.^{37,38} To obtain a definitive diagnosis, histopathologic examination is still needed in most cases of dogs with small intestinal disease.^{17,39}

Table 1. Medications Used in Treating Lundehund Gastroenteropathy

Drug	Dose	Use
Medium-chain triglyceride oil	1–2 ml/kg/day PO	To increase caloric content of food when long-chain fatty acids are restricted
Cobalamin	See Table 2	To treat cobalamin deficiency
Folic acid	10 µg/kg PO q24h	To treat folate deficiency
Tylosin	25 mg/kg PO q12h	To treat IBD and SIBO
Metronidazole	10–20 mg/kg PO q12h for 2–4 wk	To treat IBD and SIBO
Oxytetracycline	20 mg/kg q8h or q12h	To treat IBD and SIBO
Prednisone	2 mg/kg PO q12h for 1 wk, then 1 mg/kg PO q12h for 6 wk, then taper to lowest possible maintenance dose	To treat IBD; as an immunosuppressant or antiinflammatory
Azathioprine	2 mg/kg PO q24h for 2 wk, then every other day for 2 weeks, then taper to 1 mg/kg every other day	To treat IBD; as an immunosuppressant or antiinflammatory
Dolasetron	0.3–0.6 mg/kg IV or SC q12–24h	As an antiemetic
Metoclopramide	0.2–0.5 mg/kg PO, SC, or IV q8–24h	As an antiemetic

Endoscopic Imaging and Gastrointestinal Biopsy

Endoscopy is often performed on patients with GI disease for which a definitive diagnosis is unclear, and it can yield valuable information regarding the site and severity of the lesions. In the only study on endoscopy in a Lundehund, the authors reported gastropathy and enteropathy characterized by abnormal retention of food in the stomach and hyperemia of the gastric mucosa and a granular appearance of the duodenal mucosa, respectively.⁵ The authors did not specify where in the stomach the lesions were observed. These results should be viewed only as preliminary because a larger number of Lundehunds must be investigated to evaluate the significance and prevalence of these findings in this breed.

GI biopsies can be obtained through endoscopy or laparotomy, each of which has advantages and disadvantages.⁴⁰ Obtaining biopsies during endoscopy is less invasive, usually requires a shorter anesthesia time, and is associated with less risk compared with surgery.^{22,40} It also allows sampling of many biopsies and enables the clinician to evaluate the sampling sites before biopsy so that mucosal lesions that are not visible from the serosal surface can be specifically targeted if the gastroenteropathy appears to have a patchy distribution, thus minimizing the risk of missing affected areas.^{22,40} The disadvantages are that certain areas of the intestine, such

as the jejunum, cannot be reached with an endoscope, and it can be difficult to obtain samples of sufficient quality to allow a histopathologic diagnosis of intestinal lymphangiectasia, which is mainly present in the submucosa or muscular layers of the intestinal wall rather than in the mucosa.

Surgical procedures allow biopsy of any area of the GI tract as well as full-thickness biopsies that are often of better diagnostic quality than endoscopically obtained ones.⁴⁰ In general, if the clinician suspects that lymphangiectasia is present, a surgical biopsy may be necessary to confirm the diagnosis, but the increased risks associated with surgery should be considered.

TREATMENT

In all cases of Lundehund gastroenteropathy, the treatment is symptomatic because an underlying, treatable cause has not been identified. No single therapeutic plan is ideal in all cases, and individual dogs seem to respond differently to various approaches (Table 1). No controlled studies using different treatment strategies have been conducted in Lundehunds; therefore, scientific statistical data regarding response or remission rates are not available.

Diet

In general, affected Lundehunds should be fed a highly digestible, low-fat, high-quality protein diet to

relieve the absorptive load on the intestinal lymphatic system. Medium-chain triglycerides have historically been fed because some may be absorbed by a nonlymphatic route, decreasing the burden on the lymphatic system.^{41,42} However, this has not been verified in Norwegian Lundehunds with gastroenteropathy.

Vitamins

Vitamin supplementation can be of value, especially if the serum cobalamin concentration is low. Supplementation often dramatically improves the health of dogs with chronic small intestinal disease. Given the chronic nature of Lundehund gastroenteropathy, lifelong vitamin supplementation is likely to be necessary.

Cobalamin

Cobalamin must be administered parenterally because enteral absorption is compromised and insufficient to treat cobalamin deficiency. The recommended initial weekly dose is 250 µg SC for dogs weighing up to 11 lb (5 kg) and 500 µg SC for heavier dogs. Once the serum cobalamin concentration has normalized, it may be maintained within the normal range by monthly injections (Table 2).

Folate and Folic Acid

Folate deficiency can almost always be rectified by folic acid supplementation (10 µg/kg/day PO).

Other Vitamins

In dogs with chronic GI disease, serum concentrations of other vitamins, such as vitamins A, D, E, and K, may be decreased as well. However, this has not been studied in Lundehunds with gastroenteropathy.

Antibiotics

Antibiotic therapy may be helpful in some affected Lundehunds, probably because of their increased predisposition to SIBO.²¹ Tylosin, metronidazole, or oxytetracycline at standard doses may be useful adjuncts in treating Lundehund gastroenteropathy.

Immunosuppressants and Antiinflammatories

Immunosuppressants and/or antiinflammatories, such as prednisone, prednisolone, or azathioprine, are frequently used and may have to be given for extended periods to control clinical signs in Lundehunds. The exact mechanism of action of these drugs is unclear, although their effect is most likely due to a combination of antiinflammatory action, which controls conditions such as IBD, and immunosuppression, which prevents the intestinal immune system from overreacting. In the case of prednisolone, a certain stimulatory effect on enterocytes could also be beneficial.⁴³ Prednisolone has been shown to induce an increase in jejunal and ileal absorptive capacity and to lead to an increased synthesis of brush-border and membrane proteins in rats, thus assisting repair of damaged mucosa.⁴³ No controlled studies have investigated the use of azathioprine in dogs with GI disease.

Octreotide and Antiplasmin Therapy

Some of the new therapies for intestinal lymphangiectasia and PLE in humans include administration of octreotide (a somatostatin analogue) and antiplasmin. It is not fully understood how octreotide acts as a treatment in intestinal lymphangiectasia, but it is thought to reduce intestinal blood and lymph flow and inhibit triglyceride absorption, thereby relieving clinical signs.⁴⁴

Antiplasmin treatment with tranexamic acid has been successfully used in humans with increased tissue fibrinolytic activity, which can cause PLE by increasing vascular permeability.^{45,46} No studies regarding the use of octreotide or tranexamic acid in dogs with PLE have been conducted; therefore, the therapeutic value of these products is unclear. Patients with hypoproteinemia due to PLE may also be antithrombin III deficient and, therefore, in a hypercoagulable state, which may theoretically increase the risk for thromboembolic disease when antifibrinolytic agents are administered. These patients may benefit from low-dose aspirin (0.5 mg/kg PO q24h).

Other Palliative Treatments

Further symptomatic treatment may include temporary administration of diuretics when ascites or subcuta-

Table 2. Cobalamin Supplementation in Norwegian Lundehunds: Recommended Doses and Time Regimens

Body Weight	Dose (μg SC)/Follow-up
<5 kg (<11 lb)	250
5–15 kg (11–33 lb)	500
Time Regimen (wk)	
1–6	Once/wk
7–12	Once every 2 wk
16	One additional injection
20	Recheck serum cobalamin concentration

neous edema is present. Antiemetic medications, such as dolasetron or metoclopramide, can be used if the dog exhibits frequent vomiting or nausea.

PROGNOSIS

The prognosis for patients with Lundehund gastroenteropathy is variable and greatly depends on the patient's response to treatment. The disease is often progressive and can eventually lead to death due to severe panhypoproteinemia and generalized debility. Treatment should be attempted using antiinflammatories and/or immunosuppressants as well as supportive care to improve the clinical signs, but complete remission often cannot be achieved in affected patients. Some Lundehunds require lifelong intermittent treatment to control clinical signs while maintaining a good quality of life, whereas others cannot recover from the initial onset of the disease. Unfortunately, survival data are unavailable due to the lack of scientific long-term studies and the rarity of this breed, but we are currently monitoring a large number of Lundehunds in North America to acquire long-term data.

OUTLOOK

Further studies are needed and under way to understand the cause and pathogenesis of Lundehund gastroenteropathy. The cause of PLE must be investigated to identify efficacious treatment strategies. Until the nature of the underlying defect is identified, diagnostic and therapeutic possibilities are limited.

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ARTICLE #1 CE TEST



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I. Norwegian Lundehunds frequently develop

- | | |
|---------|------------------|
| a. PLE. | c. pancreatitis. |
| b. EPI. | d. hepatitis. |

2. _____ are the most common clinical signs of **Lundehund gastroenteropathy**.
- Weight loss and increased appetite
 - Vomiting and weight loss
 - Vomiting, diarrhea, weight loss, and ascites
 - Flatulence and diarrhea
3. **Which parameters are useful in assessing patients with suspected Lundehund gastroenteropathy?**
- $F\alpha_1$ -PI concentration
 - serum albumin, globulin, and total protein concentrations
 - serum cobalamin and folate concentrations
 - all of the above
4. **Which serum protein concentration usually declines first in Lundehunds with GI disease?**
- globulin
 - albumin
 - total protein
 - the albumin and globulin concentrations decrease simultaneously
5. **Which serum or blood parameter abnormality often occurs in Norwegian Lundehunds with gastroenteropathy?**
- leukocytosis
 - a decrease in the serum cTLI concentration
 - hypocalcemia
 - an elevated liver enzyme concentration
6. _____ appears to be the major cause of the low serum total calcium concentration in Lundehunds.
- Malabsorption
 - Malnutrition
 - Vitamin D deficiency
 - Loss of protein-bound calcium
7. **Serum cobalamin and folate concentrations can be abnormal as a result of small intestinal malabsorption or other conditions, especially EPI. Therefore, which serum parameter(s) should also be determined when evaluating serum cobalamin and folate concentrations?**
- serum pancreatic lipase immunoreactivity
 - serum cTLI concentration
 - serum calcium concentration
 - liver enzyme activities
8. **Which section(s) of the GI tract is most commonly affected in Lundehund gastroenteropathy?**
- the stomach and small intestine
 - the small and large intestines
 - the small intestine
 - the entire GI tract
9. **Which histopathologic change(s) can be detected from GI biopsies in Lundehunds?**
- chronic atrophic gastritis
 - intestinal lymphangiectasia
 - lymphoplasmacytic enteritis and villus atrophy
 - all of the above
10. **Which is not indicated in treating Lundehund gastroenteropathy?**
- cobalamin supplementation
 - diuretics
 - pancreatic enzymes
 - glucocorticoids