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TITLE OF CASE <i>Do not include "a case report"</i>
Hereditary selective cobalamin malabsorption and concurrent pancreatitis in a young Border Collie
SUMMARY <i>Up to 150 words summarising the case presentation and outcome (this will be freely available online)</i>
<p>A one year old male neutered Border Collie presented with failure to gain weight, lethargy, intermittent leukopenia, borderline anaemia and intermittent gastrointestinal symptoms. He was diagnosed with pancreatitis based on a blood results and abdominal ultrasonography and hereditary selective cobalamin malabsorption based on hypocobalaminaemia, methylmalonic aciduria and genetic testing for cubilin mutation. The dog responded to oral cobalamin supplementation with resolution of clinical signs and normalisation of serum cobalamin. There was no recurrence of signs after 27 months of follow-up. An association between organic acidaemias and pancreatitis has been reported in humans but to the authors' knowledge, this is the first report of hereditary selective cobalamin malabsorption and concurrent pancreatitis in a dog. Furthermore, this is the first report of inherited canine cobalamin deficiency responding to oral cobalamin supplementation.</p>

BACKGROUND *Why you think this case is important – why did you write it up?*

Hereditary selective cobalamin malabsorption has previously been described in Border Collies^{1,2,3,4,5,6}, Giant Schnauzers^{7,8}, Shar Peis^{9,10}, Beagles^{11,12,13,14,15,16} and Australian Shepherds¹⁷. Classical clinical signs include lethargy, neurological signs and failure to thrive. The condition closely resembles selective intestinal cobalamin malabsorption (Imerslund-Grasbeck syndrome) in humans^{18,19}.

Pancreatitis is the most common condition of the exocrine pancreas in dogs. The majority of cases are classed as idiopathic, although other postulated causes include hypertriglyceridaemia, endocrinopathies, adverse drug reactions, prior surgery, infections and high fat diets²⁰. An association between MMA acidaemia and the development of pancreatitis has been documented in the human literature but not yet reported in dogs^{21,22}. The mechanism is unknown, although it has been suggested that inhibition of mitochondrial function and free radical formation may play a role²¹.

CASE PRESENTATION *Presenting features, clinical and environmental history*

A one year old male neutered Border Collie was referred for investigation of an 8-month history of failure to gain weight, lethargy and intermittent gastrointestinal symptoms (anorexia, vomiting and diarrhoea). Investigations performed by the referring veterinary surgeon included faecal analysis, haematology, biochemistry, trypsin-like immunoreactivity (TLI), folate and cobalamin measurements and abdominal ultrasound (Tables 1 and 2).

Measurement (reference range)	23/12/2014	07/05/2015	17/08/2015
Haematocrit (37-55%)	32.9	37	45.5
Reticulocytes (10-110 K/ μ L)	28	40.6	39.1
White cell count (5.5-16.9 x 10 ⁹ /L)	4.24	4.32	3.04
Neutrophils (3-12 x 10 ⁹ /L)	1.79	2.10	1.10
Lymphocytes (0.5-4.9 x 10 ⁹ /L)	1.79	1.60	1.36
Monocytes (0.3-2 x 10 ⁹ /L)	0.38	0.48	0.51

Eosinophils (0.1-1.49 x 10 ⁹ /L)	0.25	0.13	0.06
Basophils (0-0.1 x 10 ⁹ /L)	0.04	0.01	0.01
Platelets (175-500 K/ μ L)	115	516	422

Table 1: Haematology results obtained prior to referral (abnormal results in bold)

Measurement (reference range)	23/12/2014	07/05/2015	17/08/2015
Glucose (4.28-8.34 mmol/L)	5.78	4.06	5.39
Urea (2.5-10.4 mmol/L)	4.3	6.4	8.6
Creatinine (27-106 μ mol/L)	71	71	62
Phosphate (1.65-3.36 mmol/L)	2.07	1.81	1.52
Total calcium (1.95-3.15 mmol/L)	2.43	2.38	2.38
Total protein (48-72 g/L)	57	50	55
Albumin (21-36 g/L)	26	27	28
Globulin (23-38 g/L)	30	23	27
ALT (8-75 U/L)	56	38	66
ALP (46-337 U/L)	131	207	313
Total bilirubin (0-14 μ mol/L)	<2	9	3
Cholesterol (2.58-10.32 mmol/L)	2.99	2.99	2.55
TLI (6.1-35 μ g/L)		21.3	
Folate (8.2-13.5 μ g/L)		11.9	
Cobalamin (\geq 275 ng/L)		<150	
Spec CPL (\leq 200 μ g/L)		89	

Table 2: Biochemistry, TLI, folate, cobalamin and spec CPL results obtained prior to referral (abnormal results in bold)

Persistent leukopenia, neutropenia and borderline anaemia, as well as hypcobalaminaemia were documented prior to referral. Faecal analysis and abdominal ultrasound (performed by a board-certified radiologist) were unremarkable. Clinical improvement with a combination of low fat diet (Royal Canin Gastrointestinal Low Fat) and metronidazole treatment was noted. The dog did not receive cobalamin or multivitamin supplementation prior to referral. The patient was referred because his symptoms recurred. Physical examination at the referral centre revealed the dog to be thin (body condition score 2/9) and depressed. His mucous membranes were pink but tacky.

Thoracic auscultation was unremarkable and he displayed cranial abdominal discomfort on palpation. He was normothermic.

INVESTIGATIONS *If relevant*

Haematology, biochemistry, urinalysis, basal cortisol, TLI, folate, cobalamin and bile acid stimulation test were obtained (Tables 3 and 4).

Measurement	Value	Reference range
White blood cell count	8.68	6-17 x 10 ⁹ /L
Neutrophils	4.30	3-11.5 x 10 ⁹ /L
Lymphocytes	3.3	1-4.3 x 10 ⁹ /L
Monocytes	0.69	0.2-1.5 x 10 ⁹ /L
Eosinophils	0.35	0.1-1.3 x 10 ⁹ /L
Basophils	0.01	0-0.5 x 10 ⁹ /L
Red blood cell count	5.94	5.5-8.5 x 10 ¹² /L
Haematocrit	38.7	37-55%
Platelets	158	175-500 x 10 ⁹ /L

Table 3: Haematology results on presentation (abnormal results in bold)

Measurement	Value	Reference range
Sodium	145	135-155 mmol/L
Potassium	4	3.6-5.7 mmol/L
Chloride	111	103-120 mmol/L
Urea	5.1	2.5-7.4 mmol/L
Creatinine	81	34-136 umol/L
Glucose	5.6	3.4-5.6 mmol/L
Total protein	54	55-77 g/L
Albumin	28	25-41 g/L
Globulin	26	24-47 g/L
Calcium	2.36	2.2-2.9 mmol/L
Phosphate	1.67	0.8-1.73 mmol/L
ALT	57	14-67 IU/L
AST	504	12-49 IU/L
CK	213	42-206 IU/L
GGT	6	0-10 IU/L
ALP	211	26-107 IU/L
Total bilirubin	5.3	0-12 umol/L
Cholesterol	3	3.3-6.5 mmol/L
Triglyceride	0.5	0.4-1.3 mmol/L
Amylase	1619	256-1609 IU/L
Lipase (DGGR)	525	0-200 IU/L
C-reactive protein	2.6	0-8.2 mg/L
TLI	>50	6.1-35 µg/L
Folate	7.9	3-13 ng/ml
Cobalamin	286	200- ng/L
Post-prandial bile acids	8	0-22.5 umol/L
Basal cortisol	163	29-250 nmol/L

Table 4: Biochemistry, TLI, folate, cobalamin, post-prandial bile acids and basal cortisol on presentation (abnormal results in bold)

Haematology was unremarkable. A serum biochemical profile documented mild hypoproteinaemia (54 g/L; 55-57) and hypocholesterolaemia (3 mmol/L; 3.3-6.5) considered secondary to gastrointestinal loss. He had elevated concentrations of aspartate aminotransferase (AST) (504 IU/L; normal 12-49), creatine kinase (CK) (211 IU/L; normal 42-206), alkaline phosphatase (ALP) (211 IU/L; normal 26-107) and 1,2-o-dilauryl-rac-glycero-3-glutaric acid (DGGR) lipase (525 IU/L; 0-200). Urinalysis documented mild proteinuria (urine protein:creatinine ratio 0.72; normal 0-0.4), bilirubinuria (+++), haematuria (++) and urine specific gravity was 1.032. Urine sediment examination and culture were negative. Cobalamin was at the bottom end of the normal range (286 ng/L (200-)). TLI was >50 µg/L consistent with pancreatic inflammation. Basal cortisol, folate and bile acid stimulation test results were within normal limits. Abdominal ultrasound was performed and documented a markedly enlarged right pancreatic limb with surrounding hyperechoic mesentery consistent with pancreatitis (Figure 1). During hospitalisation, the patient became persistently bradycardic so an ECG examination was obtained before and after 0.02mg/kg intramuscular atropine administration (Figures 2 and 3). This showed abolition of sinus bradycardia with administration of atropine.

DIFFERENTIAL DIAGNOSIS *If relevant*

Differentials for hypocobalaminaemia include dietary insufficiency of vitamin B12, small intestinal bacterial overgrowth (due to utilisation of cobalamin by intestinal microorganisms), intestinal disease leading to malabsorption, inborn error of cellular cobalamin metabolism, pancreatitis, exocrine pancreatic insufficiency or hereditary selective cobalamin malabsorption. Inborn errors of cellular cobalamin metabolism are an important cause of cobalamin deficiency in children, but not in dogs. Dietary deficiency has not been shown to lead to clinical signs of cobalamin deficiency in dogs and cats^{23,24}, however, vegetarian and vegan diets have been shown to be cobalamin deficient²⁵. Differentials for methylmalonic aciduria inborn errors of cobalamin malabsorption, postprandial and hereditary selective cobalamin malabsorption.

TREATMENT *If relevant*

The patient was initially treated with intravenous Lactated Ringers at 4ml/kg/hour, 1 mg/kg subcutaneous maropitant (Cerenia, Zoetis, UK) SID, 0.02 mg/kg intravenous buprenorphine (Vetergesic, Alstoe, UK) IV QID, 2 mg/kg intravenous ranitidine (Zantac, Glaxo Wellcome, UK) BID and 10 mg/kg PO paracetamol (Pardale, Dechra, UK) BID.

OUTCOME AND FOLLOW-UP

The patient was discharged after 6 days following supportive treatment for pancreatitis. Cobalamin was subsequently re-measured four weeks after initial presentation and was subnormal (<150 pg/ml), despite clinical improvement (Table 5).

Measurement (reference range)	07/05/2015	19/08/2015	22/09/2015	19/10/2015	24/11/2015	18/03/2016	27/09/2017
Cobalamin (>=275 ng/L)	<150	286	<150	373	489	>1000	974

Table 5: Sequential cobalamin measurements for this patient. Cobalamin supplementation was commenced following the documentation of hypocobalaminaemia in September 2015

A urine sample was submitted to the Metabolic Genetic Screening Laboratory, University of Pennsylvania for a MMA spot test which was positive consistent with methylmalonic aciduria. Hypocobalaminaemia was treated with 500µg cyanocobalamin PO SID. A DNA test was obtained to assess for mutation of the CUBN gene (Animal Health Trust, United Kingdom) and the patient was homozygous for the genetic mutation consistent with a diagnosis of Imerslund-Grasbeck syndrome. Cobalamin levels were re-measured 730 days after starting cobalamin supplementation and were 974 ng/L (ref >275). A repeat MMA urine test was not performed. Telephone consultation with the owner 27 months after initial presentation reported that the dog was very well in himself with no recurrence of clinical signs and he now weighed 20kg (Figures 4 and 5).

DISCUSSION *Include a very brief review of similar published cases*

This is the first report of pancreatitis associated with hereditary selective cobalamin malabsorption in a dog. Diagnosis of Imerslund-Grasbeck syndrome was made on the basis of a combination of low serum cobalamin concentrations, methylmalonic aciduria, DNA testing, age and breed of the dog and excellent clinical response to cobalamin supplementation. An interesting

aspect of this case was the initial serum cobalamin levels at presentation in spite of low concentrations measured by the referring vet. Serum cobalamin levels do not always correlate with body stores²⁶. Dogs with serum cobalamin in the low normal range of the reference interval and concurrently increased serum MMA have been previously reported, suggesting a cobalamin deficiency at the cellular level^{3,27}. However, dogs with early hypocobalaminaemia (eucobalaminaemia and elevated MMA) tend to be subclinical. Interestingly, MMA concentrations in healthy Border Collies have been shown to be significantly higher than healthy control dogs consistent with benign methylmalonic aciduria³. It is unlikely that the high MMA in the presence of eucobalaminaemia reflected benign methylmalonic aciduria, given the genetic testing results. MMA values in sick Border Collies with Imerslund-Gräsbeck syndrome in the literature that had not received cobalamin supplementation were always high (range 1800-6665 mmol/mol creatinine; reference range <4.2, or 1731-9142 mg/g creatinine; reference range <10)^{1,2,3,4,5}. Quantification of MMA aciduria was not confirmed in this case which would have been useful given that Border Collies with hereditary cobalamin malabsorption tended to have much higher MMA values³ and would have decreased the risk of a false positive result. However, the spot test has been shown to be useful in humans with no false positives documented in healthy patients and patients with other organic acidaemias²⁸.

Hereditary cobalamin deficiency was confirmed in this case who was homozygous for mutation in the CUBN gene. This is an autosomal recessive trait in Border Collies and the mutation in the CUBN gene encoding cubilin (CUBN:c.8392delC variant). This is a single base pair deletion predicted to cause frame shift and premature stop codon in CUBN gene. The carrier frequency of this mutation in Border Collies is 6.2%²⁹. Dietary cobalamin is released and binds to R-protein and enters the duodenum. In the duodenum, the R protein-cobalamin complex is broken down by pancreatic proteases and cobalamin binds to intrinsic factor (IF) (produced in the stomach and pancreas of dogs). Cobalamin-IF complex is then absorbed by specific receptors (the cubam

receptor consisting of 2 separate subunits: amnionless (AMN) and cubilin (CUBN)) on the enterocytes in the ileum⁵. Ileal absorption is impaired in Border Collies due to the mutation in the CUBN gene. Cobalamin is required for the conversion of homocysteine to methionine and for the conversion of methylmalonyl coenzyme A to succinyl CoA; this results in accumulation of plasma homocysteine and methylmalonic acid and the development of elevated plasma homocysteine levels and methylmalonic aciduria^{1,5,30}. Urea cycle dysfunction and hyperammonaemia have also been described in dogs leading to neurological signs^{1,31} but were not reported in this case.

The patient had clinical signs consistent with cobalamin deficiency: - failure to gain weight, lethargy and intermittent gastrointestinal signs and anorexia^{4,12}. Weight loss occurs because decreased methionine synthase levels can lead to a deficiency in active folate which can impair DNA replication, particularly in rapidly dividing cells. This can lead to malabsorption of nutrients and reduced food intake^{4,31}. Interestingly, the patient had a bradyarrhythmia which was reversible with atropine; bradyarrhythmias have previously been documented in dogs with selective cobalamin malabsorption^{4,11}. They are also recognised in humans and are thought to occur due to dysfunction of the autonomic nervous system³².

Haematological abnormalities are commonly reported in cobalamin deficiency and were intermittently present in this dog although, cobalamin deficiency in Border Collies is not always associated with haematological abnormalities⁴. Haematological abnormalities commonly reported in cobalamin deficient dogs include normocytic normochromic anaemia and neutropenia^{4,12}. This patient had historical evidence of neutropenia and borderline low PCV. Biochemical abnormalities noted in this case included mild hypoproteinaemia and hypocholesterolaemia which could reflect intestinal malabsorption. Elevated AST (as seen in this case) has been shown to correlate with elevated homocysteine levels in patients with cobalamin deficiency and is thought to reflect increased metabolic activity⁴. Mildly elevated ALP was likely reactive (however,

increased bone turnover due to young age could also be contributing) and elevated DGGR lipase was considered due to pancreatitis. Hyperlipasaemia has been associated with prior corticosteroid use, however, this patient had not received steroids prior to referral. Mild proteinuria (as noted in this case) is well documented in dogs with selective cobalamin malabsorption^{2,3,5,7,12}. This is thought to occur due to the absence of Cubam complex receptors in renal tubular cells which results in reduced albumin reabsorption³³.

6-73% of dogs with chronic enteropathies have concurrent hypocobalaminaemia^{34,35,36,37,38}. Elevated MMA concentrations are also seen in approximately 25% of these cases³⁸. The mechanism for cobalamin deficiency is due to damage to the ileal mucosal receptors for binding of cobalamin-intrinsic factor complexes³⁹. It is impossible to exclude significant gastrointestinal inflammation and malabsorption as a concurrent cause of hypocobalaminaemia in this case, however, the compatible genetic testing, the resolution of clinical signs and weight gain in the long-term after receiving only treatment with cobalamin, make this less likely. Furthermore, there was only a short duration of gastrointestinal signs and an absence of hypoalbuminaemia. All dogs with hypocobalaminaemia due to gastrointestinal disease in one study had concurrent hypoalbuminaemia²⁷.

Pancreatitis was diagnosed in this case by a combination of clinical signs, elevated DGGR lipase and TLI and abdominal ultrasound findings consistent with pancreatitis (enlarged and hypoechoic pancreas with surrounding hyperechoic mesentery). Pancreatitis can affect dogs of any age, but the majority of dogs are middle-aged to old so to diagnose pancreatitis in this dog at one year old was unusual and adds weight to the association with cobalamin deficiency²⁰. Although the clinical signs of cobalamin deficiency and pancreatitis are similar, abdominal pain is not a recognised clinical sign of cobalamin deficiency. The patient responded to symptomatic treatment for pancreatitis and was only diagnosed with and treated for hereditary cobalamin malabsorption 4 weeks after initial presentation which is suggestive that the dogs presenting clinical signs were

due to pancreatitis. There is an association between MMA organic acidaemias and pancreatitis in children^{21,22}. These cases had inherited disorders of organic acid metabolism. None of these cases had Imerslund-Gräsbeck syndrome. Some of the cases in the human literature had chronic pancreatitis and therefore it is also possible that this case had chronic pancreatitis, however, this would not be possible to confirm without histology⁴⁰. Proposed mechanisms discussed in the human literature include inappropriate pancreatic enzyme activation and the inability of the pancreas to withstand metabolic stresses that are normally encountered. Inhibition of mitochondrial function and free radical formation may play a role²¹. We postulate that this case represents pancreatitis which was an effect of cellular cobalamin deficiency rather than the cause of cobalamin deficiency, given that this case had documented hereditary cobalamin deficiency and the pancreatitis did not recur after effective supplementation. However, there have been reports of human pernicious anaemia (leading to cobalamin deficiency) leading to the development of small intestinal changes and therefore the potential that cobalamin deficiency itself can lead to primary manifestations of gastrointestinal disease⁴¹. Furthermore, there is a postulated association between hyperhomocysteinaemia and the development of pancreatitis in humans due to its role in vascular dysfunction, microthrombosis and inflammatory conditions therefore it is also possible that elevated homocysteine levels (due to cobalamin deficiency) could have triggered pancreatitis in this case⁴². Therefore, it is also reasonable to suggest that pancreatitis could have resulted directly from a cobalamin deficiency. The association between MMA acidaemia and pancreatitis is interesting in this case, however, the lack of follow-up MMA to confirm resolution of MMA acidaemia with treatment for pancreatitis, is a significant limitation. However, the patient did not have any further episodes of pancreatitis in a two-year follow up period following successful treatment of cobalamin deficiency.

Oral cobalamin treatment has been shown to be effective in dogs with hypocobalaminaemia due to chronic enteropathies³⁹. Oral cobalamin in human cobalamin deficiency has also been shown to be effective^{43,44,45,46}. It is thought that in humans approximately 1% of free cobalamin is absorbed across the small intestine by passive diffusion, independently of intrinsic factor⁴⁴ which might

explain the response to treatment in this dog. Adequate response to treatment is documented by a combination of increased cobalamin and decreased MMA⁸. We were able to document persistent cobalamin levels within the normal range in this dog with over 2 years of follow-up.

The limitations of this study include the fact that methylmalonic aciduria was not quantified by organic acid gas chromatography and was not re-measured to document resolution following cobalamin supplementation. Homocysteine concentrations were not measured; hyperhomocysteinaemia has been reported in dogs with cobalamin deficiency^{5,27} and would be interesting to explore further, given the potential causal association with pancreatitis.

The outcome in this case was excellent with complete resolution of clinical signs following cobalamin supplementation. Furthermore, over a two-year follow-up period, the patient did not have any recurrence of pancreatitis. This suggests an excellent prognosis for dogs with pancreatitis due to cobalamin deficiency, provided that the cause is identified and treated and stresses the importance of considering this as a differential diagnosis for pancreatitis in a young dog of a susceptible breed.

LEARNING POINTS/TAKE HOME MESSAGES 3 to 5 bullet points – this is a required field

- Cobalamin deficiency should be considered as a cause of failure to thrive and concurrent pancreatitis in young Border Collies
- Hereditary selective cobalamin malabsorption can be diagnosed by genetic testing
- Pancreatitis may be caused by methylmalonic aciduria in dogs
- Hereditary selective cobalamin malabsorption can be successfully treated with oral cobalamin supplementation.

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FIGURE/VIDEO CAPTIONS *figures should NOT be embedded in this document*

Figure 1: Abdominal ultrasound image documenting an enlarged right pancreatic limb with surrounding hyperechoic mesentery.

Figure 2: ECG recording documenting sinus bradycardia.

Figure 3: ECG recording following intramuscular administration of atropine documenting abolition of sinus bradycardia.

Figure 4: Patient before diagnosis of hereditary selective cobalamin malabsorption

Figure 5: Patient following resolution of pancreatitis and institution of cobalamin supplementation.

OWNER'S PERSPECTIVE *Optional*

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