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# Case Report: Hypocobalaminemia and Coat Discoloration in A Dog

**Keywords:** Canine; Cobalamin; Vitamin B12 Deficiency; Coat Discoloration; Hair Depigmentation; Chronic Diarrhoea

## Abstract

Hypocobalaminemia is a common complication in case of chronic diarrhoea in dogs. Reduced cobalamin (vitamin B12) causes diarrhoea, creating a viscous circle.

A 10-year-old male intact Frisian pointing dog (18.9 kg; BCS 4/9) was presented to the primary care veterinarian diarrhoea. After 6 months of chronic diarrhoea with symptomatic treatments, lab analysis showed a reduction of cobalamin (145 pmol/L; reference 173-599) and folic acid (18.5 nmol/L; reference 21.1-54.0). Consistent with hypocobalaminemia, a nonregenerative anaemia was found.

Treatment consisted of weekly injections of 1 mg vitamin B12 (for 6 weeks) and the months of supplementation per os. Six months after the treatment, the discoloration was resolved.

The mechanism of coat discoloration due to hypocobalaminemia is unclear, but multiple cases in humans are known. Vitamin B12 is supposed to influence melanin to impact the coat colour. To the authors' knowledge, this is the first case in dogs of hypocobalaminemia resulting in coat discoloration.

Open Access Case Report

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## Introduction

Cobalamin, vitamin B12, is an essentialwater-soluble vitamin. It functions as a cofactor for both homocysteine methyl transferase and methylmalonyl-CoA mutase. Primary, the cytosolic homocysteine methyltransferase is facilitating the conversionof homocysteine to methionine, which also requires folic acid as cofactor. Following this pathway, pyrimidines and purinescan be produced for DNA and RNA synthesis. Secondary, the mitochondrial methylmalonyl-CoA mutase is involved in the enzymatic degradation of fatty acids. Consequently, cobalamin is essential for myelin synthesis, haematopoiesis, and DNA synthesis [1-4].

The gastrointestinal absorption of vitamin B12 is complex, consequently a hypocobalaminemia is comprehensible. During digestion, three indispensable steps are compulsory. Firstly, in the stomach, cobalamin is separated from dietary protein by gastric pepsin and bound to protect haptocorrin from bacterial fermentation. Secondly in the small intestine, cobalamin is separated from haptocorrin by pancreatic proteases and forms a complex with intrinsic factor (IF). Indogs, IF is primarily produced in the pancreas. Thirdly, the complex of IF and cobalamin absorbed via active transport in the distal ileum. Plants contain practically no cobalamin since their enzymes do not depend on this vitamin; all vitamin B12 in animal feed originates either from animal products or from bacterial fermentation. Nonetheless, the location of absorptionoccurs proximal of the site of bacterial fermentation in dogs. Consequently, all cobalamin produced by bacterial fermentation is excreted in the faeces. Due to the complexity of the absorption and the essential role of the exocrine pancreas and the limited absorption area, hypocobalaminemia can be initiated by gastrointestinal disease. Particularlyin case of exocrine pancreatic insufficiency and severe chronic ileal disease can lead to hypocobalaminemia [2-4].

The clinical pathologic symptoms for dogs with low vitamin B12 typically concentratein two areas: blood cell abnormalities and neurological signs. Megaloblastic nonregenerative anaemia, hypersegmented neutrophils,and neutropenia, are signs ofearlyhypocobalaminemia in dogs. Secondary, diarrhoea, vomiting, anorexia and lethargy can be observed. Since cobalamin (as well as folic acid) deficiency can result in signs of vomiting and diarrhoea, a vicious circle can occur. Hence, veterinarians should be alert to the possibility of vitamin B12 deficiency in case of chronic diarrhoea, both primary and secondary [4].

The current case report describescoat discoloration in a dog with hypocobalaminemia. The aim of this paper is to present the potential pathophysiological correlation between vitamin B12 and coat colour in dogs.

## Materials and Methods

A 10-year-old male intact Frisian pointing dog (18.9 kg; BCS 4/9) was presented to the primary care veterinarian with acute small bowel diarrhoea. Other signs included: vomiting, reduced appetite and lethargy. Neurological abnormalities or signs of malabsorption were not present.

## Results

First treatment by the primary care veterinarian was symptomatic with maropitant. The original food (i.e.,HillsTM prescription diet®j/d canine) was not changed.Six months after first presentation, the gastrointestinal problems worsened: daily vomiting and diarrhoea. Both vomiting and diarrhoea was without blood incorporation. Additionally, a clear discolouration of the coat appeared see (Figure 1). The treatment consisted of omeprazole / maropitant and food change to HillsTM prescription diet®i/d canine chicken. Secondary to this treatment, the dog was medicated withcarprofen continuously for osteoarthritis.

Two weeks laterthe symptoms did persist, so extensive blood analysis was performed (Table 1), apart from continuation of thesymptomatic treatment. Metronidazole was added to the treatment plan, even though the giardia analysis was negative. Additionally, the dog was treated orally with milbemycin/preziquantel every quarter and was negative for faecal parasites.

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**Figure 1:** A dog with coat discoloration due to hypocobalaminemia. Left: After 6 months of diarrhoea (before treatment). Right: 6 months after start of treatment.

**Table 1:** Relevant blood analysis values after 6 months of symptoms

| Blood parameter | Value | Range |
|---|---|---|
| Red blood cell count (RBC) | 4.60 x10^12/L | 5.65 - 8.87 |
| Hematocrit (HCT) | 15.00% | 37.3 - 61.7 |
| Hemoglobin (HGB) | 9.2 g/dL | 13.1 - 20.5 |
| Mean cell volume erythrocytes (MCV) | 32.5 fL | 61.6 - 73.5 |
| Mean cell hemoglobin in erythrocytes (MCH) | 20.0 pg | 21.2 - 25.9 |
| Mean cell hemoglobin concentration in erythrocytes (MCHC) | 61.4 g/dL | 32.0 - 37.9 |
| Red-cell distribution width (RDW) | 25.60% | 13.6 - 21.7 |
| Reticulocytes (RETIC) | 97.2 K/µL | 10.0 - 110.0 |
| Platelets (PLT) | 570 K/µL | 148 - 484 |
| Mean platelet volume (MPV) | 8.6 fL | 8.7 - 13.2 |
| Platelet volume distribution width (PDW)P | 13.9 fL | 9.1 - 19.4 |
| Plateletcrit (PCT) | 0.49% | 0.14 - 0.46 |
| Vitamin B12 (Cobalamin) | 145 pmol/L | 173 - 599 |
| Vitamin B9 (Folic acid) | 18.5 nmol/L | 21.1 – 54.0 |
| Total protein | 46 g/L | 52 - 82 |
| Albumin | 17 g/L | 22 - 39 |

The lab analysis showed that both cobalamin (145 pmol/L; reference 173-599) and folic acid (18.5 nmol/L; reference 21.1-54.0) were reduced. Consistent with hypocobalaminemia, a nonregenerative anaemia was found.

After six months of having diarrhoea with symptomatic treatment, the treatment against hypocobalaminemia was started: the dog was treated weekly with 1 mg vitamin B12 injections (6 weeks) and supplementation per os (3 months). Three weeks after starting the vitamin B12 injections, the diarrhoea was cured. Subsequently, the coat discolorationwasresolved6 months later see (Figure 1).

## Discussion

The primary cause of diarrhoea remains indefinit. Adverse effects of NSAIDs have been reported in multiple and commonly included vomiting, diarrhoea, and anorexia [5] which wasqual to the observed signs. However, the administration of carprofen has not been changed while the clinical signs weren solved. However, carprofen combined with omeprazole has shown to induce faecal dysbiosis and increase intestinal inflammatory markers in otherwise healthy dogs [6]. This coadministration of both medicines could have contributed to the continuation of the diarrhoea and thereby adding to the demised absorption of vitamin B12. Still, omeprazole has only been given 6 months after the first representation. Subsequently, these treatments cannot be diagnosed as the primary cause of the diarrhoea.

Dogs with vitamin B12 deficiency show a variety of signs such as anorexia, lethargy, diarrhoea, nonregenerative anaemia, and neurological signs [4]. All clinical signs, except for the neurological abnormalities, were present. With respect to blood parameters, the serum level of cobalamin is no sufficient evidence for a conclusive diagnosis. The intracellular shortage of vitamin B12 results in a lower enzyme activity rather than the level in the serum. To correlate serum values to intracellular levels, a raise in methylmalonic acid or an increased homocysteine level in serum can be used for diagnosis. It has to be considered that reduced homocysteine level can be analysed in case of a folate deficiency [4,7]. Sinceboth folic acid and cobalamin showed decreased serum values, a primary hypocobalaminemia based on blood values alone wasinconclusive. Secondary analysis of methylmalonic acid and homocysteine could be used to confirm the diagnosis. Additionally, the additional serum measurementscould contribute to a differentiation between a deficiency of cobalamin and folic acid; methylmalonic acid is not influenced by a folic acid deficiency. Retrospectively, the vitamin B12 injections proved successful without supplementation of folic acid, proving the hypocobalaminemia as true by therapeutic diagnostics.

With respect to coat discoloration, no cases have been reported in dogs to the author's knowledge.In humans, reversible hyperpigmentation of the skin and depigmentation of the hair has been reported in some cases of vitamin B12 deficiency. In case reported by [8], vitamin B12 substitution resulted in normalizing serum B12 levels and a decrease of skin hyperpigmentation, but hair depigmentation remained. Histopathological findings showed increased levels of melanin in the basal layer of the epidermis in these patients. However, the exact underlying mechanism remain unknown in humans as well, especially due to the apparent contradictory depigmentation of the hair versus the hyperpigmentation of the skin persists to be ambiguous.

Deposited melaninis responsible for hair and skin pigmentation. Melanin is produced by melanocytes, whereafter melanin-containing granules (melanosomes) are exported to neighbouring keratinocytes. The skin pigmentation is the result of melanin in these keratinocytes. [9,10]. In hair follicles, the keratocytes containing melanin form the pigmented hair shaft [11]. A single melanocyte can serve 40 keratinocytes. The density of melanocytes is similar in humans for all skin types, but the amount of melanin and the type of melanin determines the colouration [10,12].

Two main types of melanin can be found in skin and hair: pheomelanin (red/yellow colour) and eumelanin (brown/black colour). The ratio of both melanin types is determined by three factors: (1) thetyrosinase activity, (2) the concentration of cysteine as a constituent ofpheomelanin, and (3) the concentration of tyrosine as a component of eumelanin.While tyrosine/cysteine influence the formation of both its end products, an increased tyrosinase activity turns up the level of eumelanin [10,12].

Lower levels of B12 have been shown to cause premature greying of hair in humans, once again without known mechanism.

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[13]. It has been hypothesized that vitamin B12 deficiency decreases the level of glutathione. Glutathione is an essential non-enzymatic antioxidant in mammalian cells which consists of three amino acids: cysteine, glycine, glutamate [14]. Pheomelanin generation utilizes the cysteine from glutathione. This reduction of glutathione stores makes melanocytes more susceptible to oxidative stress and might lower the total production of eumelanin and pheomelanin. On the other hand, melanin is also a potent antioxidant scavenging free radicals [10]. With a potential lower level of glutathione and casual oxidative stress, melanin could serve as antioxidant.

## Conclusion

In conclusion, even though the mechanism of coat discoloration in correlation to hypocobalaminemia remains unclear, multiple cases in humans have presented the impact of vitamin B12 on hair discoloration. Vitamin B12 is supposed to influence melanin to impact the coat colour. To the authors' knowledge, the coat discoloration because of hypocobalaminemia has not yet been described in dogs.

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