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# Immunoglobulins and acute phase proteins in Van cats - associations with sex, age, and eye colour

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**Abstract:** It was aimed to determine concentrations of plasma immunoglobulins (IgG, IgA, IgM) and acute phase proteins (α-1 acid glycoprotein, serum amyloid A, ceruloplasmin) and the association of these parameters with age, sex, and eye colour in Van cats. Blood plasma of healthy, forty-seven Van cats (Van Cat Home) fed with standard cat food were involved in the study. Cats were divided into four groups based on age (<1, 2 to 2.5, 3 to 4, > 5) and eye colour (amber-amber, amber-blue, blue-amber, and blue-blue eyes described from left to right), and two groups based on sex (male and female). Plasma IgG, IgA, IgM, α-1 acid glycoprotein, serum amyloid A, and ceruloplasmin concentrations were determined, and the concentrations were found to be 2.20 ± 0.05 mg/mL, 1.05 ± 0.04 mg/mL, 2.52 ± 0.18 mg/mL, 562.00 ± 14.27 µg/mL, 1.49 ± 0.03 µg/mL, and 2.88 ± 0.13 mg/dL, respectively. Male Van cats had higher IgA levels than the female cats ($P < 0.05$). α-1 acid glycoprotein concentrations in cats under 1-year-old were higher from that in the other age groups, whereas the significant difference was obtained compared to 2 to 2.5-year-old cats ($p < 0.05$). IgM concentrations were higher in cats with blue-blue eye colour than in the cats with other eye colours, while statistically significant difference was observed only cats with amber-blue eye colour ($p < 0.05$). Amber-amber eyed cat plasma ceruloplasmin concentrations were higher from that in the other eye coloured cats while significant difference was determined compared to amber-blue eyed cats ($p < 0.05$). Plasma immunoglobulins and acute phase proteins were determined and the associations of these parameters with age, sex, and eye colour were examined for the first time in Van cats. These data are thought to be important as reference levels in terms of diagnosis and prognosis.

**Key words:** Acute phase proteins, eye colour, sex, immunoglobulins, Van cat

## 1. Introduction

Turkish Van cat originates from eastern Turkey (Van province). The most characteristic feature of Van cat is the colour of its eyes: both eyes blue, one eye blue one eye amber (dyschromatopsia), or both eyes amber. Another impressive feature is that it is known to be the only cat breed that loves swimming [1]. Unfortunately, nowadays, the number of Van cats is gradually decreasing, and they are facing the danger of extinction [2]. The first scientific studies of Van cats were held in 1992 by Inan (distribution of eye pigment) [3] and Eksen et al. (hematological parameters) [4]. In addition, the biochemical studies of this breed were found in a few studies [5–9]. In a study conducted on blood groups, A blood group was found to be 40%, and B blood group was found to be 60% in Van cats [5]. In the same study, the percentages of A and B blood groups in Ankara cats were determined as 53.6% and 46.4%, respectively, and differences between the breeds were revealed. Altunok et al. [6] reported that phosphogluconate dehydrogenase, malic enzyme, and esterase D loci were different in Van cats from that in the other cat breeds. Some of the biochemical parameters during pregnancy and lactation periods have changed in Van cats [7]. Özkan et al. [8] reported higher creatinine levels in male Van cats than in the females. Aluminum, barium, copper, manganese, and strontium were significantly higher in male Van cats compared to that in the females. Also, aluminum, copper, lithium, strontium, and zinc levels showed differences within the eye colour [9].

Determination of biochemical parameters in the blood is crucially important for clinicians to evaluate diagnosis, differential diagnosis, and prognosis of the diseases in terms of human and animal health [10–13]. Many investigators are in agreement with the idea that biochemical parameters in blood and tissue fluids may change under the influence of factors such as age, sex, season, race, and stress [11,14–19]. Also, it is considered

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to be the most appropriate approach to determine the reference intervals to represent the race [5,8,20–23]. Plasma creatinine concentrations were higher in Birman cats than in cats of other breeds [20]. A breed effect was demonstrated for plasma glucose, urea, creatinine, total protein, albumin, calcium, potassium, total $CO_2$, and activity of alanine aminotransferase (ALT) in cat breeds of Holly Birman, Chartreux, Maine Coon, and Persian [22]. Paltrinieri et al. [23] determined high α2-globulin concentrations in Abyssinian cats; high serum creatinine, α2-globulin and glucose concentrations in Holly Birman cats; low β2-globulin and γ-globulin concentrations in Norwegian Forest and Siberian cats, and they suggested that breed-specific reference intervals should be used for these parameters. Age (for plasma concentration of glucose) and body weight (for concentrations of phosphates, albumin, creatinine, glucose, and total proteins) associations were reported in domestic shorthair (DSH) cats by Reynolds et al. [21], who suggested that the findings should not be adapted to other cat breeds.

Immunoglobulins (Ig), which derived from the plasma cells differentiated from B-lymphocytes, are of glycoprotein structure and serve as antibodies in response to immunogens. Wood et al. [24] revealed that circulating IgG levels increased over time after feline immunodeficiency virus infection (FIV), whereas IgA levels, in general, did not change in domestic cats. Very few data are found in animals regarding the association of Ig levels with factors such as age, sex, and race. In a study established in DSH adult (2–5 years) and senior (10–14 years) cats, IgM and IgA levels were found to be lower in the adults (both sexes) than in the senior group, whereas IgG levels were shown to be unchanged [16].

Acute-phase proteins (APP) are known to be synthesized primarily in liver and increase in certain circumstances such as infectious diseases, surgical interventions, traumas, and acute-phase response in humans and animals. Acute-phase proteins begin to increase within a few hours after inflammation, peaks in 24–48 h, and remains elevated as long as the inflammatory stimulus persists. α1-acid glycoprotein (AAG), C-reactive protein (CRP), ceruloplasmin (Cp), and serum amyloid A (SAA) are among the inflammatory markers used in human and various animals [25]. C-reactive protein is specially used to evaluate the acute-phase response of dogs, whereas AAG is considered as a more suitable marker for cats [26]. α1-acid glycoprotein plays an important role in the diagnosis of feline infectious peritonitis (FIP) and may also be useful in the studies of FIP pathogenesis [27,28]. Serum amyloid A levels are reported to increase in FIP, diabetes, renal failure, and urinary tract diseases in cats [27,28,29]. However, there is insufficient information on the changes of APP with other factors such as age, sex, and eye colour in cats; one study reported that SAA and haptoglobin levels did not change with age in DSH cats [16].

In the literature search, because of insufficiency of the data of different cat breeds and the inability to find information about the relevant parameters in Van cats, it is thought that this information obtained from the endangered Van cats will be scientifically and clinically valuable. As levels of plasma Igs and APPs may vary between breeds and this difference is considered as important in the diagnosis and prognosis of diseases, it was aimed to determine plasma concentrations of Igs (IgG, IgA and IgM) and APPs (AAG, SAA and Cp) and also the association of these parameters with age, sex, and eye colour in Van cats, which were fed in a controlled environment with standard conditions.

## 2. Materials and methods

### 2.1. Animal and study design

Blood plasma from forty-seven healthy Van cats, which were housed in Van Cat Home (Yüzüncü Yıl University, Van, Turkey), was used. The cats were fed with standard cat food (LA-CAT, Israel) in standard conditions. The animals were divided into four groups based on age (<1, 2 to 2.5, 3 to 4, and > 5 years) and eye colour (amber-amber, amber-blue, blue-amber, and blue-blue eyes described from left to right) and two groups based on sex (male, female). Blood samples were taken from the cephalic vein into EDTA tubes at 10:00 am, and their plasma was removed by centrifugation at 3000 rpm for 15 min. Plasma samples were stored at –80 °C until the analysis.

### 2.2. Laboratory measurements

Immunoglobulin G, IgM and IgA, AGG, and SAA concentrations in plasma samples were determined by feline ELISA kits (Sunred, Shanghai Sunred Biological Technology Co., Ltd) according to the manufacturer's instructions by an ELISA reader (BioTek Instruments, μQuant, U.S.A), with a microplate (Greiner bio-one Italia, Cellstar, Italy). Ceruloplasmin concentrations were analyzed manually by colourimetric method. Briefly, plasma samples were incubated with p-phenylenediamine dichloride in optimum acetate buffer. The enzymatic oxidation of p-phenylenediamine dichloride results in the formation of a pink product with the maximum absorption at 546 nm in spectrophotometer (UV 2100 UV–vis recording spectrophotometer, Shimadzu, Japan). Ceruloplasmin concentration was calculated using the formula reported by Colombo and Richterich [30].

### 2.3. Statistical analysis

All the values were expressed as mean ± SEM. The results of groups were analyzed by Student's t-test (sex) and ANOVA (age and eye colour) with posthoc Duncan test (SPSS for

Windows, release 23.0, IBM Corp., Armonk, NY, USA). A $p$ value < 0.05 was considered statistically significant.

## 3. Results

Plasma IgG, IgA and IgM, AAG, SAA, and Cp concentrations of Van cats are presented in Table 1, and their differences regarding the variables (age, sex and eye colour) are presented in Tables 2, 3, and 4.

Plasma IgG, IgA, IgM, AAG, SAA and Cp concentrations were 2.20 ± 0.05 mg/mL, 1.05 ± 0.04 mg/mL, 2.52 ± 0.18 mg/mL, 562.00±14.27 µg/mL, 1.49 ± 0.03 µg/mL and 2.88 ± 0.13 mg/dL, respectively. Plasma AAG concentrations in cats under 1-year-old were higher from that in the other age groups, whereas the significant difference was obtained compared to 2 to 2.5-year-old cats ($p$ < 0.05). When examined in terms of sex, male cats had higher IgA concentrations than that of female cats ($p$ < 0.05). In terms of the eye colours, blue-blue eyed cat plasma IgM concentrations were higher from that in the other eye coloured cats, whereas the significant difference was determined compared to amber-blue eye colour group ($p$ < 0.05). Amber-amber eyed cat plasma Cp concentrations were higher from that in the other eye coloured cats, whereas significant difference was determined compared to amber-blue eyed group ($p$ < 0.05).

## 4. Discussion

In general, for monitoring the health status and prognosis of the diseases, species-specific reference values are evaluated, since it is difficult to determine the biochemical values of races. However, determination of the reference intervals to represent the race was suggested [8,18,19,20,22,23].

**Table 1.** Plasma immunoglobulin and acute phase protein concentrations of the Van cats (Mean ± Standart Error) and reference values in cats.

| | **IgG**(mg/mL) | **IgA**(mg/mL) | **IgM**(mg/mL) | **AAG**(µg/mL) | **SAA**(µg/mL) | **Cp**(mg/dL) |
|---|---|---|---|---|---|---|
| **Van Cats (n = 47)** | 2.20 ± 0.05 | 1.05 ± 0.04 | 2.52 ± 0.18 | 562.00 ± 14.27 | 1.49 ± 0.03 | 2.88 ± 0.13 |
| | 2.14–20.00 [a, b,c,d,e] | 0.22–2.60 [a,b,c] | 0.17–6.30 [a, b,c,e] | 483.00–1200.00 [e,f,g] | 0.38–18.56 [b,e,f,h,i] | 1.50–8.60 [j] |

References: a: Ackley et al.[35]; b: Campbell et al.,[16]; c: Harley et al. [36]; d: Tizard, [37]; e: Giordino et al., [27]; f: Tuna et al., [41]; g: Kann et al., [31]; h: Vilhena et al. [43]; i: Kann et al., [44]; j: Andrews et al. [46].
IgG: immunoglobulin G; IgA: immunoglobulin A; IgM: immunoglobulin M; AAG: α1-acid glycoprotein; SAA: serum amyloid A; Cp: ceruloplasmin.

**Table 2.** Immunoglobulins and acute phase proteins of the Van cats according to the age differences (Mean ± Standart Error).

| **Age** | **IgG** (mg/mL) | **IgA** (mg/mL) | **IgM** (mg/mL) | **AAG** (µg/mL) | **SAA**(µg/mL) | **Cp**(mg/dL) | **n** |
|---|---|---|---|---|---|---|---|
| < 1 | 2.36 ± 0.10 | 1.03 ± 0.09 | 2.45 ± 0.28 | 602.53 ± 18.02[a] | 1.56 ± 0.06 | 3.31 ± 0.37 | 11 |
| 2 to 2.5 | 2.14 ± 0.08 | 1.08 ± 0.08 | 2.80 ± 0.50 | 505.62 ± 18.32[b] | 1.44 ± 0.07 | 2.95 ± 0.28 | 11 |
| 3 to 4 | 2.14 ± 0.08 | 1.06 ± 0.06 | 2.54 ± 0.33 | 564.86 ± 28.06[ab] | 1.49 ± 0.06 | 2.61 ± 0.20 | 15 |
| > 5 | 2.28 ± 0.14 | 1.10 ± 0.11 | 2.21 ± 0.41 | 583.74 ± 43.05[ab] | 1.48 ± 0.09 | 2.90 ± 0.15 | 10 |

[ab]: Differences in the same column are statistically significant ($p$ < 0.05).
IgG: immunoglobulin G; IgA: immunoglobulin A; IgM: immunoglobulin M; AAG: α1-acid glycoprotein; SAA: serum amyloid A; Cp: ceruloplasmin.

**Table 3.** Immunoglobulins and acute phase proteins of the Van cats according to the sex differences (Mean ± Standart Error).

| **Sex** | **IgG** (mg/mL) | **IgA** (mg/mL) | **IgM** (mg/mL) | **AAG** (µg/mL) | **SAA** (µg/mL) | **Cp** (mg/dL) | **n** |
|---|---|---|---|---|---|---|---|
| Female | 2.17 ± 0.07 | 0.98 ± 0.05[b] | 2.66 ± 0.21 | 568.23 ± 18.08 | 1.48 ± 0.04 | 3.02 ± 0.18 | 31 |
| Male | 2.26 ± 0.07 | 1.16 ± 0.06[a] | 2.27 ± 0.34 | 552.56 ± 23.10 | 1.51 ± 0.06 | 2.63 ± 0.11 | 16 |

[ab]: Differences in the same column are statistically significant ($p$ < 0.05).
IgG: immunoglobulin G; IgA: immunoglobulin A; IgM: immunoglobulin M; AAG: α1-acid glycoprotein; SAA: serum amyloid A; Cp: ceruloplasmin.

**Table 4.** Immunoglobulins and acute phase proteins of the Van cats according to the eye colour differences (Mean ± Standart Error).

| **Age** | **IgG** (mg/mL) | **IgA** (mg/mL) | **IgM** (mg/mL) | **AAG** (µg/mL) | **SAA** (µg/mL) | **Cp** (mg/dL) | **n** |
|---|---|---|---|---|---|---|---|
| BB | 2.31 ± 0.08 | 1.02 ± 0.04 | 3.09 ± 0.43$^{a}$ | 569.46 ± 26.27 | 1.49 ± 0.07 | 2.89 ± 0.20$^{ab}$ | 11 |
| BA | 2.04 ± 0.12 | 1.00 ± 0.10 | 2.32 ± 0.33$^{ab}$ | 546.42 ± 36.23 | 1.44 ± 0.06 | 2.63 ± 0.13$^{ab}$ | 12 |
| AB | 2.15 ± 0.11 | 1.04 ± 0.07 | 1.88 ± 0.26$^{b}$ | 543.78 ± 27.18 | 1.57 ± 0.08 | 2.57 ± 0.21$^{b}$ | 10 |
| AA | 2.30 ± 0.09 | 1.11 ± 0.10 | 2.67 ± 0.37$^{ab}$ | 563.28 ± 16.08 | 1.51 ± 0.06 | 3.35 ± 0.34$^{a}$ | 14 |

$^{ab}$: Differences in the same column are statistically significant ($p < 0.05$).
IgG: immunoglobulin G; IgA: immunoglobulin A; IgM: immunoglobulin M; AAG: α1-acid glycoprotein; SAA: serum amyloid A; Cp: ceruloplasmin; BB: blue blue; BA: blue amber; AB: amber blue; AA: amber amber.

As it would be ideal to determine reference intervals by a properly designed study under controlled conditions, this study was conducted in 47 Van cats obtained from Van Cat Home in order to ensure standard conditions. It is thought that the identification of normal values of some Igs and APPs will give important information to clinicians and researchers in terms of monitoring the health status and also diagnosis and prognosis of the diseases such as FIP [27,28], FIV [31,32], feline leukemia virus infection (FeLV) [33], urinary tract diseases [29], pancreatitis and pancreatic tumor [34].

To the best of our best knowledge, no study was reported on serum Ig and APP concentrations of Van cats. Campbell et al. [16] reported IgG, IgA and, IgM levels in 101 healthy 2 to 4-year-old DSH cats as 2.14 ± 0.18, 0.22 ± 0.03 and 0.17 ± 0.02 mg/mL, respectively, whereas Ackley et al. [35] reported IgG, IgA, and IgM levels in 14 healthy domestic cats as 15.1 ± 6.6, 1.5 ± 0.10, and 0.90 ± 0.17 mg/mL, respectively. Harley et al. [36] reported IgG, IgA, and IgM levels in 14 DSH and Abyssinian cat hybrids as 19.08 ± 5.38, 2.60 ± 2.06, and 2.04 ± 0.83 mg/mL, respectively. Tizard [37] reported IgG levels in cats between 4–20 mg/mL. The IgG levels obtained in this study were lower from the levels presented by Harley et al. [36] and Ackley et al. [35] whereas, showed compliance with the levels reported by Campbell et al [16]. In the present study, there was no difference between the ages in terms of IgG. Similarly, Campbell et al. [16] reported that IgG levels in 2 to 4-year-old DSH cats did not differ from 10 to 14-year-old senior cats. They, however, determined that IgA and IgM levels were higher in 10 to 14-year-old senior cats than in the 2 to 4-year-old cats. We found that IgA and IgM levels were consistent with the literature (Table 1) and there was no difference between the ages in terms of IgA and IgM. This may be due to differences in age ranges and breed differences.

In the literature search, no study has been encountered reporting the association of Ig levels with sex in cats. In sheep above 4 months, IgG, IgA, and IgM levels were reported to be lower in females than in the males [14]. In humans, IgA levels were higher in males than in the females, whereas IgG and IgM levels were lower in the males [38]. In this study, higher IgA levels obtained from male Van cats are compatible with sheep and human data. This result seems to be remarkable. Lower Ig A levels in females may be related to estradiol; in overiectomized rats, estradiol administration resulted in a significant decline in cervicovaginal content of IgA in a dose dependent manner, and it was suggested that hormonal balance in females may affect the immune response of the reproductive tract [39].

When examined with respect to eye colour, IgM levels were higher in cats with blue-blue eye colour than in the cats with other eye colours. Studies on the eye colour of Van cats are limited: Altunok et al. [40] reported that plasma glucose levels were higher in blue-blue eyed Van cats than in other eye-coloured groups (blue-amber, amber-blue, amber-amber). Serum aluminum, copper, manganese, strontium, and zinc levels were higher in blue-blue eyed Van cats than in the other eye-coloured cats [9]. These data obtained from Van cats suggest that further studies need to be performed in Van cats with blue-blue eye colour.

Acute-phase proteins are synthesized primarily in the liver as a result of the stimulation of cytokines synthesized by immune cells during inflammation. Serum amyloid A is considered to be the precursor of amyloid protein A, the major protein of α-amyloid protein. Serum amyloid A is one of the major acute-phase proteins in cats with AAG, and its serum levels increase (10-100 fold) in certain cases such as infection, inflammation, injury, hospitalization, and neoplasm [26]. In cats, AAG concentrations are reported to be 512.48 ± 183.95 µg/mL, 483.0 ± 166.7 and 1200 ± 620 µg/mL [27,31,41]. The AAG concentrations obtained in the present study were in the literature data range. α1-acid glucoprotein concentrations were reported to be increased in FIP [27]. Determination of higher concentrations of AAG in cats under 1-year-old compared to 2-2.5 years-old cats, would be worth considering clinical importance, as clinical FIP is usually seen in cats aged especially 6 months to 2 years [42].

Serum SAA concentrations in healthy cats are reported in a wide range: Vilhena et al. [43] reported as 0.38–0.40 µg/mL in 10 healthy cats from different breeds, yet Tuna

et al. [41] (1.94 ± 1.34 µg/mL) and Kann et al. [44] (1.80 ± 2.30 µg/mL) reported higher levels. On the other hand, Campbell et al. [16] reported SAA concentrations in DSH cats to be 18.56 ± 3.60 µg/mL, and Giordano et al. [27] reported 10.21 ± 8.32 µg/mL in healthy cats (a group of 11 DSH cats and 13 Persian cats). The findings of this study were higher than the result of Vilhena et al. [43], and lower than the result of Tuna et al. [41] and Kann et al. [44]. No difference was determined between the ages in terms of SAA concentrations. Similarly, Campbell et al. [16] reported that SAA concentrations in 2 to 4-year-old DSH cats did not differ from those in 10 to 14-year-old cats.

Ceruloplasmin is the main transporter of copper in human plasma and maintains approximately 90%–95% of the total copper circulating in healthy individuals. It is mainly synthesized in the liver, and an APP that shows a moderate response in cases of inflammation and tissue damage [45]. There are limited data on Cp concentrations in cats: Andrews et al. [46] reported Cp concentrations in the range of 1.5–8.6 mg/dL in 40 healthy cats. In the present study, the values obtained from Van cats were found to be consistent with the obtained data. To our knowledge, no data was reported on Cp concentrations in terms of age, breed, and sex in cats. Ceruloplasmin concentrations did not change in humans between the ages of 20 and 89 years, and Cp concentrations in women were higher than in men [47]. In another study, older man, and women had higher Cp concentrations than in the juniors [48]. In this study, except eye colour, there was no difference regarding age and sex in Van cats. It is thought that the difference between the eye colours regarding this parameter should be examined in detail with further studies.

## 5. Conclusion

With this study, plasma IgG, IgA, IgM, SAA, AAG, and Cp concentrations were determined for the first time in Van cats. Male Van cats had higher IgA levels than in the female cats. Plasma AAG concentrations in cats under 1-year of age were higher from 2 to 2.5-year-old cats. IgM concentrations were higher in cats with blue-blue eye colour than in the cats with amber-blue eye colour. Amber-amber eyed cat plasma ceruloplasmin concentrations were higher that in the amber-blue eyed cats. Van cat is a specific breed; therefore, these data, especially AAG and SAA concentrations obtained in this breed, are thought to be important as reference levels in terms of diagnosis, prognosis, and treatment protocols. In addition, it is recommended to examine the association of age, sex, and eye colour with the other parameters.

## Approval of the ethics committee

The present study was submitted to the Ethical Committee of the Experimental Animal Production and Research Center of the Veterinary Faculty of Selçuk University and was approved under the protocol number 2017-44.

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