Hyperproteinaemia in cats and dogs: An approach to diagnostic investigation

Increased serum protein concentrations can be associated with inflammatory, infectious and neoplastic conditions. Hyperproteinaemia is a significant biochemical finding in both dogs and cats that warrants further investigation. Due to the wide range of differential diagnoses it is essential that a systematic approach to the investigation of hyperproteinaemia is implemented in order to identify the underlying aetiology. This article will discuss the diagnostic approach to hyperproteinaemia and the potential differential diagnoses.

Key words: Hyperproteinaemia, monoclonal gammopathy, polyclonal gammopathy, serum protein electrophoresis

Introduction

Albumin and globulins account for the majority of the plasma proteins. Albumin is a large osmotically active protein which accounts for approximately 75% of colloid oncotic pressure (COP) (McGrotty et al. 2016). Globulins comprise of a heterogeneous group of proteins that include immunoglobulins (a.k.a. antibodies), acute phase proteins (APPs) and enzymes. Immunoglobulins (IgG, IgM, IgA and IgE) account for the largest component of globulins. They are synthesised by cells of B-lymphocyte lineage, mostly differentiated B cells known as plasma cells, in response to antigenic stimulation. Globulins are also involved in drug transport and contribute to COP. Fibrinogen and clotting factors are also present within plasma, but are removed during the clotting process that forms serum.

If identified during the investigation of clinical disease in cats and dogs, increased serum or plasma protein concentrations (hyperproteinaemia) is a useful and significant finding that warrants further investigation. Hyperproteinaemia can be associated with either reduced whole body water levels (i.e. volume contractions due to dehydration) or increased serum protein production due to a variety of inflammatory, infectious and/or neoplastic conditions.

Serum protein electrophoresis (SPE) is a laboratory technique used to separate the serum protein into measurable fractions. SPE can differentiate proliferation of a single plasma cell or B-lymphocyte (monoclonal gammopathy) from proliferation of multiple plasma cell lineages (polyclonal gammopathy). This distinction can allow the clinician to prioritise their list of differential diagnoses accordingly.

This article will discuss the differential diagnoses for hyperproteinaemia and how to conduct a methodical investigation to characterise the underlying aetiology.

Characterising the hyperproteinaemia

Artefact vs. true

Following the detection of hyperproteinaemia it is important to consider whether the result could be attributed to laboratory artefact. Measurement techniques based on refractometry or wet chemistry are both subject to error. A lipaemic or, to a lesser extent, a haemolysed sample can cause an artefactual increase in the measured serum protein concentration. In addition, with some analysers, the presence of hyperbilirubinaemia may result in an artefactual increase in the measured serum protein concentration.

Relative vs. absolute

Once true hyperproteinaemia has been established the investigation can proceed to differentiate between a relative or absolute hyperproteinaemia (Figure 1).

In relative hyperproteinaemia there is a proportional increase in all protein fractions such that the albumin and globulin ratio is normal. Typically, albumin concentration is increased above the reference interval,
with or without elevations in globulins. This form of hyperproteinaemia is often accompanied by erythrocytosis and possibly pre-renal azotaemia. It occurs as a result of haemoconcentration (i.e. dehydration leading to reduced whole body water levels) and will resolve following correction of fluid deficits. In the clinical setting there may be a history of increased fluid losses (e.g. vomiting; diarrhoea; polyuria) or reduced water intake (e.g. water deprivation). Physical examination findings may reveal evidence of dehydration (e.g. dry mucus membranes; skin tent).

In absolute hyperproteinaemia there is increased production of either globulin or (rarely) albumin, resulting in an abnormal albumin to globulin ratio. Absolute hyperproteinaemia secondary to hyperglobulinaemia occurs as a result of increased globulin production due to inflammation, infection or neoplasia. In many cases there is also a ‘compensatory’ hypoalbuminaemia. A single case report describes absolute hyperproteinaemia secondary to hyperalbuminaemia in a dog with a massive hepatocellular carcinoma (Cooper et al. 2009). In this case there were no clinical or clinicopathological findings consistent with dehydration or haemoconcentration, and the hyperalbuminaemia resolved following surgical removal of the neoplasia. Physical examination findings relating to increased blood viscosity (i.e. hyperviscosity syndrome) may be seen in dogs and cats with hyperproteinaemia. These include bleeding diathesis, hypertension, retinopathy and neurological abnormalities.

The greater the degree of hyperproteinaemia the more significant the finding and the greater the need for further investigation. Mild hyperglobulaemia is frequently encountered with many chronic infectious and inflammatory diseases. Moderate to severe hyperglobulinaemia is more frequently associated with chronic systemic infection or lymphoproliferative disorders. The history, physical examination and clinicopathological findings, including serum protein electrophoresis, should be considered together to allow prioritisation of the list of differential diagnoses (Table 1).

**Electrophoresis**

Electrophoresis is a relatively inexpensive, specialist laboratory technique that can be applied to both serum and urine proteins. Proteins are separated according to their physical properties (size, mass and electrical charge) by application of an electrical charge across a strip of agarose gel or cellulose acetate. Separated proteins are stained and their density measured, resulting in a graphical trace (a.k.a. electrophoretogram; Figures 2 and 3A-D). Capillary gel electrophoresis has more recently been described as an alternative method. The shape of the electrophoretogram can be evaluated and the approximate protein concentrations for each fraction calculated from the percentage density and total protein concentration.

**Serum Protein Fractions**

Serum proteins are separated into six fractions: albumin and alpha-1 (α1), alpha-2 (α2), beta-1 (β1), beta-2 (β2), and gamma (γ) globulins (Figure 2).

**Albumin fraction**

In the healthy cat or dog, albumin is the largest protein fraction of serum, it is demonstrated on the electrophoretogram in Figure 2 as the tallest band.

**Alpha-globulin fraction**

The α1-globulin fraction includes: protease inhibitor α1-antitrypsin; APP α1-acid glycoprotein; and lipid transport protein α1-lipoprotein. This fraction can be increased with pregnancy, neoplasia and acute inflammation.

The α2-globulin fraction includes: APPs ceruloplasmin, haptoglobin and α2-macroglobulin; hormone transport protein thyroxine-binding globulin; and renin substrate angiotensinogen. This fraction can be increased in the presence of acute inflammation, nephrotic syndrome, and advanced diabetes mellitus.

**Beta-globulin fraction**

The β1-globulin fraction is primarily composed of transferrin, a negative APP.

The β2-globulin fraction includes: β-lipoproteins; complement; C-reactive protein (CRP); and some immunoglobulins (primarily IgA and IgM; occasionally IgG). This fraction can be with inflammation, neoplasia and hepatic disease.

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**Figure 1:** Initial approach to hyperproteinaemia.