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COMPARATIVE MEDICINE REVIEW OF IMMUNE-MEDIATED NEPHROTIC SYNDROME DUE TO BABESIA INFECTION.

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Abstract

Awareness regarding the need for One Health is steadily increasing. This is largely due to the zoonotic element of many diseases. The past two decades have also shown increased support for translational and comparative medicine where animals with naturally occurring non-communicable diseases as well as zoonotic diseases that are also observed in humans are studied to advance both veterinary and human medicine. Understanding renal disease progression and possible means of diagnosis as well as treatment to prevent end-stage renal failure is critical to both human and veterinary medicine. Nephrotic syndrome is of particular interest due to its challenging progression and associated proteinuria/albuminuria, which if left untreated may rapidly lead to end-stage kidney failure or death by related physical complications. Nephrotic syndrome may be caused by an immune cascade from parasitic infections such as *Babesia* infection. *Babesia* is progressively becoming a global zoonotic concern for humans, including associated immune-mediated renal disease. Due to the large number of companion and feral animals infected with *Babesia*, the disease process and associated complications, such as nephrotic syndrome and acute liver failure are more fully understood in these species. This review aims to explore immune-mediated nephrotic syndrome due to *Babesia* infection in companion animals and developments in diagnosis and treatment as well as the applicability to human medicine. Advancement in urine analysis for glomerular and tubule injury biomarkers as well as the detection of immunoglobulins in urine shows promise as a less invasive means of diagnosis than renal biopsy in small and very ill patients. Further research on felines with immune-mediated nephrotic syndrome may deliver valuable information for both veterinary and human medicine and may also provide transferable insights to large human and feline populations with immunodeficiency.

Keywords: *Comparative Medicine, Veterinary Science, Nephrotic Syndrome, Babesia Infection, Renal Disease.*
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Introduction

Since the Covid-19 pandemic, there has been greater global awareness and support for One Health. This is largely due to the zoonotic element of many diseases. The past two decades have also shown increased support for translational and comparative medicine where animals with naturally occurring non-communicable diseases as well as zoonotic diseases that are also observed in humans are studied to advance both veterinary and human medicine1-5. The disease processes witnessed in animal models with naturally occurring diseases have shown to be superior in terms of knowledge and relevance to human medicine than the disease processes observed in animals in a laboratory environment purposefully infected with pathogens1,2,4. An organ of primary importance and dilemma to both human and animal medicine is the kidney. Glomerulonephritis meeting the diagnostic criteria for the nephrotic syndrome (NS) is of particular interest due to its challenging progression and associated proteinuria/albuminuria, which if left untreated may rapidly lead to end-stage kidney failure or death by related physical complications6-8. Whether in humans or animals, a clinical diagnosis requires the presence of ascites or edema, hypoalbuminemia, hypercholesterolemia, as well as proteinuria which propels disease progression6-9. This review intends to explore the disease process of glomerulonephritis and its link to NS. While any form of glomerulonephritis can potentially lead to NS, the focus that follows is on answering how an immune-mediated cause, *Babesia*, more commonly referred to as tick-bite fever, has implications for the kidney, especially the glomerular filtration system. This will be discussed about NS in companion animals with potential information for human medicine as well.

Methodology

This research employed a narrative review design and methodology. A narrative review is less linear than a

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systematic review methodology and does not require a specific prerequisite question enabling the researcher to explore the broad topic at hand70-72. While narrative reviews still provide a synthesis of literature on the topic, they do not require a reliance solely on empirical research, and therefore other forms of research and grey literature may also be explored71,72. While there is a less exact manner to this type of research, in terms of this narrative review specific research questions were still asked and certain search terms were used.

Research questions

1. What is the pathophysiology of nephrotic syndrome?
2. What is immune-mediated glomerulonephritis and how does it relate to nephrotic syndrome in companion animals and humans?
3. How does *Babesia* cause immune-mediated nephrotic syndrome?
4. What are the current means of diagnosis and treatment of nephrotic syndrome more generally and immune-mediated nephrotic syndrome more specifically?

Data collection and collation

Information relating to the research questions was gathered using the search terms "nephrotic syndrome", "glomerulonephritis", "immune-mediated nephrotic syndrome", "*Babesia* infection" "influence of *Babesia* on kidney function" "diagnosis of the nephrotic syndrome", "treatment of nephrotic syndrome", "diagnosis of *Babesia* infection", "treatment of *Babesia* infection". All search terms were repeated with "about animals", "about companion animals, and "about humans". Citations were also followed.

Search engines and electronic databases that were used included Google Scholar, Scopus, Africa Journals Online, PubMed, and EBSCOhost. The initial search spanned 2018-2023 to find the most recent advances in this area. The search was then expanded to 2013-2023 to place the research in the last decade. Finally, an open date system was employed to explore the historical developments of glomerulonephritis and nephrotic syndrome in companion animals and the relationship with *Babesia* infection.

The information was collated about the research questions and relevant themes relating to veterinary and human medicine.

Discussion

Pathophysiology of nephrotic syndrome: Where did the albumin go to?

The glomerulus, which is the main filter of the kidneys, plays a pivotal role in retaining proteins, especially albumin10,11. While albuminuria/proteinuria directs clinical attention to the glomerulus, debate as to how exactly the albumin 'escapes' is still ongoing11-13. However, most scientists agree that a problem lies with one or more of the three layers in this specialized filtration system12,14,15. Namely, the middle layer, the glomerular basement membrane (GBM) or its surrounding layers, the fenestrated endothelial cells, and the outer surface of podocytes11,12,15,16. The spaces within the endothelial layer are technically large enough to allow albumin molecules to pass through11,12,14. However, it is thought that the glycocalyx that spreads in between these cells provides a hydrostatic force against the albumin14,17. If the endothelial barrier of the glomeruli is affected when it is activated by a foreign body such as parasites or by immune complexes, this may cause the glycocalyx to shed14,17. When this happens albumin can pass through this layer14,17,18. Negatively charged albumin molecules are further repelled by the GBM12,14,17. This is a result of the extensively negative charge of the glycosaminoglycans in this membrane12,14,17,18. The glycosaminoglycans also help to maintain the glycocalyx12,14,17,18. The podocytes forming the last layer are viewed as a special slit diaphragm12,15,16. They are made up of basal (positively charged) and apical (negatively charged) membranes and contain transmembrane proteins which are responsible for transmitting signals and maintaining the function of this layer12,15,16. The foot processes are within the basal membrane and are connected to the GBM14,16-18. Anything that causes disruption or damage to any of the layers, such as parasites, the interplay of antigen and antibody complexes19, and resulting inflammation may influence the hydrostatic capabilities, negative repellent properties, or transfer of signals, which may then allow albumin through the glomerular filter.

While the endothelial cells and GBM are designed to repel albumin, this is not generally a function of the podocytes within a healthy glomerulus14,20,21. Therefore, the podocytes will view albumin as an invader and activate scavengers such as phagocytes to deal with the albumin. This interaction of the scavengers with the albumin leads to injury of the podocytes and may be part of an immune cascade, depending on the initial cause of injury to the glomerulus14,20-22. The proximal tubules will try to reabsorb this lost albumin. However, due to the excessive amount of albumin because of damage or injury to the filtration barrier, as well as inflammation, tubular damage may also occur12,14,20-22.

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The loss of albumin and resultant damage to the glomerulus is critical in NS and is key to understanding the other diagnostic symptoms6,7,10,11,20-22. This injury or damage to the glomerulus alters blood flow within the renal capillaries and influences the functioning of the sodium-potassium pump of the tubules, both of which are involved in the activation of the renin-angiotensin-aldosterone system23,24. This leads to a further release of enzymes and hormones which influence fluid retention and negatively affect the functioning of other organs23,24. The liver cells are also activated by the hypoalbuminemia and by compensation release an excess of cholesterol into the blood6,8,9,25. While not part of the diagnostic criteria for NS, clinical anorexia or cachexia as well as cardiac disturbance or cardio-renal syndrome may point to excess albumin loss and glomerular dysfunction.

Glomerulonephritis and nephrotic syndrome in companion animals

There was a concentrated focus on NS in animals during the late 1970's and early 1980's, followed by a lull until the past decade. As previously mentioned, the re-intensification may be due to a focus on One Health. However, another possibility is that with advances in kidney screening and histological practices being incorporated into veterinary medicine, research in this needed area is gaining momentum.

As cats and dogs share the same environments with humans as well as have more similar metabolic and physiological processes, knowledge about NS in these species may be the most valuable from a translational perspective. Similarly to humans, NS in dogs and cats may be idiopathic, caused by various drugs, amyloidosis, diabetes, infections, neoplasms, and immune-mediated processes9,19,21,26-30. While pancreatitis can cause acute kidney injury in both humans and animals, it is a greater cause of NS in dogs and cats31-35. Minimal change disease, focal segmental glomerulosclerosis, membranous glomerular nephropathy, and membranoproliferative glomerulonephritis are all, to varying degrees, observed causes of NS in cats and dogs19,21,36-38. However, they are often rather the histopathological classification in these animals21,39.

At this point, there are no international guidelines for classifying glomerular disease in cats. There is, nevertheless, a trend in veterinary medicine to use the canine guidelines and classify glomerular disease broadly according to immune-mediated origin and non-immune-mediated origin19,37. Minimal change disease occurs very rarely in cats or dogs, and cats experience more immune-mediated glomerulonephritis associated with membranous nephropathy6,21,40,41. There is a greater incidence in male kittens (under 4 years old). This may be due to the high prevalence of feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) in this population globally22,28. The increased incidence of feline coronaviruses that lead to feline infectious peritonitis may also be a contributing factor. Proteinuria associated with NS is particularly challenging to treat in cats as the International Renal Interest Society (IRIS) Guidelines for chronic kidney disease suggest that for survival, a 90% reduction in proteinuria is required in cats, while only 50% in dogs42. This is exacerbated by the fact that the most prescribed treatment, angiotensin-renin-enzyme inhibitors, should not be administered to dehydrated or unstable animals and does not always reduce proteinuria to nearly the required extent in cats40,42. Consequently, if another cause or disease process is inducing the NS, it needs to be discovered and treated as quickly as possible to prevent extensive glomerular damage and preserve function.

Babesia and their link to kidney disease

Babesia spp. are intra-erythrocyte parasites that are vector-borne via ticks43,44. While infection with *Babesia* species in cats is predominantly a problem of Southern Africa43,45, with few reports globally45,46, regarding humans *Babesia* are progressively becoming a global zoonotic concern47,48. This is largely due to climate change, increasing temperatures, and altered seasonal patterns47,48. Once bitten by an infected tick, the parasites enter the host's red blood cells (RBCs), spread, and cause fragmentation, leading to hemolysis. It was once believed that the parasites only entered the RBCs43,45,46. However, it has now been shown that the parasites can attach to and enter other body cells where there is extensive vasculature and may give rise to an immune-mediated cascade48-51. This is particularly problematic for vascularized organs like the kidneys where the parasites may enter the cells of the glomerulus, particularly those of the GBM, sub-endothelial cells, as well as tubules48-51. Effacement and thickening are caused both by the damage done by the parasites themselves as well as by the immune-complex reaction48-51. Children, individuals older than 50, the immunocompromised, and those with comorbidities often present with complicated infection as is seen in cats48, which includes acute renal injury often leading to death44,52-56. While *Babesia* infection in cats is primarily localized to Southern Africa, the endemic and complicated nature of the disease provides a reservoir of animal models that may shed light on the disease process in humans.

Considerations for clinical practice

Diagnostic considerations

While symptoms and evidence of a tick bite may be used for diagnosis of *Babesia* infection in humans, blood

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microscopy to confirm diagnosis is usually preferred in veterinary medicine. Severe anemia is usually witnessed in animal populations infected with *Babesia* and as such a blood transfusion is recommended. This may also be the case for some human patients and species-specific guidelines for blood typing and cross-matching should be followed. Co-infection with *Mycoplasma haemofelis* may be a likely contributing factor to anemia. However, the hemolysis caused by *Babesia* infection should not be underplayed. This hemolysis has histopathologically been found to be a contributing factor to injury to the GBM, podocytes, as well as tubules43,46,48,51-52. Relatedly, cardiac signs as well as any sign of cardio-renal syndrome should be closely monitored.

As previously mentioned, the diagnosis of NS requires the presence of ascites or edema, hypercholesterolemia, proteinuria, and hypoalbuminemia. It is imperative to note in cases where an animal or human may be dehydrated that hypoalbuminemia may be missed or not seem as serious on serum chemistry results as this may perilously preclude the diagnosis of NS. Foamy urine should also always be investigated as a possible sign of proteinuria/albuminuria. With current advances in both chemistry and light microscopy urine analysis, markers of renal injury for fairly specific areas within the kidney such as glomerulus or tubules can be identified without an invasive or risky procedure for a small patient such as a renal biopsy22,40,48-51. Relatedly, hyaline casts observed on urine analysis should also raise awareness of glomerular injury and proteinuria/albuminuria22,48-51. While increased BUN points to impaired kidney and liver function, a low creatinine result may not be expected and if evident is, nevertheless, clinically serious57. Such a result may be due to a combination of severe proteinuria as well as low body condition with anorexia. Importantly, Rossi et al.19 found that initially in immune-mediated glomerulonephritis kidney chemistry results, including symmetric dimethylarginine (SDMA), may appear normal despite changes and injury already being histologically present on the GBM and surrounding layers, and if left untreated will lead to end-stage kidney failure due to NS.

Treatment considerations

The importance of promptly treating *Babesia* infection and suppressing the related immune-complex response, whether in animals or humans, in an attempt to prevent the development of NS or end-stage kidney failure if NS is already present cannot be overemphasized. For decades histological changes associated with glomerulonephritis and in particular NS in cats and dogs6,21,58-61 as well as ruminants62-65 have been documented. However, with less advanced methods, the cause of damage remained somewhat theoretical in that immune complexes became trapped within the glomerular layers, especially the GBM21. More recently studies have confirmed the presence of immune-complexes as well as *Babesia* within the GBM, subendothelial cells, and basal membrane of podocytes19,28,48-51. This leads to what is known as complement activation whereby neutrophils, platelets, and macrophages become involved. This can lead to an immune cascade and thickening of the GBM with the development of humps referred to as spikes and increases the spaces of the podocyte diaphragm and fenestrations of the endothelial layer, all enabling albumin to pass through19,21,28,48-51. The aggravation of platelets forms thromboxanes in an attempt to prevent the immunoglobulins from dispersing within the glomerulus19,21,48. However, thromboxanes are chemotactic for neutrophils as well as they slow glomerular filtration through vasoconstriction19,21,28,48. This is aggravated by the *Babesia* itself being shown to be chemotactic to the glomerulus and inducing inflammation which can cause cells to release cytotoxic nitric oxide21,48. In addition, the platelet activation due to immune complexes as well as hemolysis caused by the *Babesia* neutralizes the negative charges of the GBM and enables albumin to 'escape'21,48. As previously discussed, the podocytes not recognizing the foreign albumin (nor parasites) activate further macrophage action which damages the foot processes and increases the spaces of the slit diaphragm14,20-22,48-51.

While steroids such as prednisone need to be used with caution in patients with kidney disease, possible liver complications, and ascites or edema, a short treatment to curtail the immune-mediated response may be imperative. Doxycycline is usually the first line of treatment for canines and humans with *Babesia* infection. While primaquine phosphate is historically the first-line treatment for *Babesia* infection in cats45, it is more nephrotoxic than doxycycline and the latter may be considered solely or in junction with primaquine phosphate, especially if there is co-infection with *Mycoplasma haemofelis.*

Supportive treatment

N3 PUFAS, glycosaminoglycans, as well as a renal-supportive diet, may support kidney function and healing. Including n3 PUFAS to reduce proteinuria/albuminuria is part of IRIS guidelines and has also been shown to alleviate hypercholesteremia in NS25,42,66-68. If liver injury is present as is often the case with *Babesia* infection as noted by the icterus and markedly increased ALT, possibly further aggravated the liver's ability to manufacture protein and contributed to the hypercholesteremia. Both n3 PUFAS and glycosaminoglycans may reduce cytokine response and down-regulate immune complexes within the glomerulus, aid the reestablishment of glycocalyx and support the

GBM's negative polarity, as well as provide liver support12,14,18,22,66,67. Further to this n3 PUFAS may assist the podocyte transmembrane layer in re-establishing a barrier and correct signalling.

Evaluation of studies used and future recommendations

Studies detailing naturally occurring glomerulonephritis, NS, and or *Babesia* infection in companion animals were often small in size or case studies, and therefore generalizability at this point is limited. However, the smaller studies of naturally occurring diseases and even the case studies often include histopathological kidney results as well as urine analysis and microscopic findings. These studies also provide a departure point and avenue for increased clinical information than induced disease research. More recent studies detail a far greater understanding of immune-mediated responses within the glomerular filtration system as well as links to specific causes such as intra-erythrocyte parasitic infections like *Babesia*, and immunosuppressive viral infections such as FIV and HIV.

While the risk of death or severe loss of kidney tissue often precludes renal biopsies in small animals, many cats and dogs in South Africa die every year due to acute end-stage renal failure secondary to *Babesia* infection. This is currently becoming an international concern in human medicine. A postmortem biopsy can be a very delicate subject with a grieving owner. However, some may consent to this procedure as well, and many feral cats present with *Babesia felis, Leo*, or *microtia* infections through welfare trap-neuter-release programs. Those that unfortunately do not survive may be suitable for postmortem renal biopsy. A more promising area for utilization in small patients with NS is the advancement in urine analysis for glomerular and tubule injury biomarkers as well as the detection of immunoglobulins in urine19,22,48-51,69. Some of the urine chemistry tests still need to be normed for cats. However, this may provide a large pool of data about specific renal areas injured due to immune-mediated and non-immune-mediated NS as well as tracing of these markers during and after treatment. Such research combined with clinical case summaries including treatment of *Babesia* infection in cats, especially when leading to immune-mediated NS, may provide valuable information for both veterinary and human medicine and may provide transferable insights to large human and feline populations with immunodeficiency immune-mediated NS. Top of Form

Conclusion

Nephrotic syndrome is an ever-present concern in both veterinary and human medicine. With increased migration of both humans and animals as well as changing seasonal patterns there is likely to be an increase in *Babesia* infections as well as *Babesia-induced* renal disease. A greater understanding of immune-mediated renal disease and more specifically immune-mediated NS may enhance the focus and design of future research studies as well as assist clinicians with prompt recognition and diagnosis with the hope of a better outcome for patients.

List of abbreviations

NS: Nephrotic syndrome
GBM: glomerular basement membrane
IRIS: International Renal Interest Society
FIV: Feline immunodeficiency virus
FeLV: Feline leukemia virus
BUN: Blood-urea-nitorgen
SDMA: Symmetric dimethylarginine

Disclosure statement

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