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Review

Steroid-responsive meningitis-arteritis: What have we learned since 2010? A narrative review

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ABSTRACT

Steroid-responsive meningitis-arteritis (SRMA) occurs as an immune-mediated, inflammatory, and non-infectious disorder of juvenile and young-adult dogs. In principle, SRMA is divided into two clinical courses: during the typical acute form, dogs are presented with fever, cervical hyperaesthesia, and reluctance to move. The more protracted form most probably emerges after insufficient immunosuppressive treatment or relapses, with additional neurologic deficits localized in the cervical and thoracolumbar spinal cord or multifocally. The trigger leading to SRMA still remains an unsolved riddle for immunologists and clinical neurologists. In the past, many attempts have been made to clarify the etiology of this disease without success. The purpose of writing this narrative review about SRMA is to summarize new insights on the pathogenesis of SRMA with a focus on immunologic dysregulation. Furthermore, unusual manifestations of the disease, new diagnostic approaches using possible laboratory biomarkers or diagnostic imaging tools, and potential innovative treatment strategies are discussed.

Introduction

Steroid-responsive meningitis-arteritis (SRMA) is a common neurologic as well as systemic disease presented with a prevalence of 1.6% (Lowrie et al., 2009b) to 2% (Fluehmann et al., 2006) in specialized neurologic services. SRMA describes the most common type of canine meningitis (Meric, 1988). Furthermore, it represents the most frequent diagnosis of dogs presented with cervical hyperaesthesia (Grapes et al., 2020) and pyrexia, including juvenile dogs up until 18 months of age (Black et al., 2019). Basically, SRMA can occur at any age, but juvenile and young-adult dogs are mainly affected by this disease between the age of 6 and 18 months (Cizinauskas et al., 2000; Tipold and Schatzberg, 2010). Exceptions are described in the literature for SRMA affected dogs ranging from 3 months (Harcourt, 1978) to 9 years of age (Cizinauskas et al., 2000).

In the majority of the literature, female and male dogs are equally affected by SRMA (Tipold and Jaggy, 1994; Cizinauskas et al., 2000; Lowrie et al., 2009a; Rose et al., 2014). However, there are two recently published studies from Germany reported a sex predisposition for male dogs, being significantly more frequently affected by SRMA questioning a regional difference in the sex distribution of the disease (62.7% (Hilpert et al., 2020) and 64.9% (Biedermann et al., 2016)).

Any dog breed can be diagnosed with SRMA, but several breeds, especially medium to large-sized dogs are overrepresented (DeLahunta and Glass, 2009; Tipold and Stein, 2010), thus suggesting the existence of a possible genetic predisposition. Classically predisposed dog breeds are Beagles (Harcourt, 1978; Ruben et al., 1989; Tipold and Jaggy, 1994), Boxers (Tipold, 1995; Behr and Cauzinille, 2006), and Bernese Mountain dogs (Presthus, 1991; Tipold, 1995; Cizinauskas et al., 2000). A study conducted by Rose et al. in 2014 in the United Kingdom confirmed the predilection for the above-mentioned breeds and further detected a predisposition for Border collies, Jack Russel terriers, and Whippets. Furthermore, an epidemiological study by Lau et al. in 2019 in the US added Korthal Griffons and Golden retrievers to the catalogue of commonly affected dog breeds (Lau et al., 2019). To complete the list, Weimaraners (Tipold and Schatzberg, 2010; Rose et al., 2014), Nova Scotia duck tolling retrievers (Anfinsen et al., 2008; Tipold and Schatzberg, 2010), Petit Basset Griffon Vendeéns (Voss et al., 2012), German shorthaired pointers (Alcoverro et al., 2019), and English Springer spaniels (Lowrie et al., 2009b) are also mentioned in several studies. Table 1 summarizes all relevant dog breeds that are frequently affected by SRMA.

Alongside the importance of SRMA in veterinary medicine, it also represents a unique translational large animal model in human medicine

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Table 1
Common dog breeds affected by SRMA.

Commonly affected dog breed	Ref.
Beagle	Harcourt, 1978 ($n = 20$);Ruben et al., 1989 ($n = 16/49$); Snyder et al. 1995 ($n = 18$);Rose et al., 2014 ($n = 5/60$); Lau et al., 2014 ($n = 6/61$)
Bernese Mountain Dog	Presthus, 1991 ($n = 11$);Tipold and Jaggy, 1994 ($n = 9/32$);Cizinauskas et al., 2000 ($n = 5/10$); Lau et al., 2014 ($n = 10/61$)
Border Collie	Rose et al., 2014 ($n = 7/60$)
Boxer	Tipold and Jaggy, 1994 ($n = 10/32$);Behr and Cauzinille, 2006 ($n = 12$);Lowrie et al., 2009b ($n = 4/20$);Rose et al., 2014 ($n = 4/60$); Lau et al., 2014 ($n = 9/61$)
English Springer Spaniel	Irving and Chrisman, 1990 ($n = 1/5$);Lowrie et al., 2009b ($n = 4/20$);Rose et al., 2014 ($n = 2/60$)
German Shorthaired Pointer	Alcoverro et al., 2019 ($n = 4/8$)
Golden Retriever	Tipold and Jaggy, 1994 ($n = 4/32$); Lau et al., 2014 ($n = 12/61$)
Jack Russel Terriers	Rose et al., 2014 ($n = 7/60$)
Nova Scotia Duck Tolling Retriever	Cizinauskas et al., 2000 ($n = 2/10$);Anfinsen et al., 2008 ($n = 9/362$);Tipold and Schatzberg, 2010 (data not available)
Petit Basset Griffon Vendeén	Voss et al., 2012 ($n = 3/9$)
Weimaraner	Irving and Chrisman, 1990 ($n = 1/5$);Tipold and Schatzberg, 2010 (data not available);Rose et al., 2014 ($n = 2/60$)
Whippets	Rose et al., 2014 ($n = 11/60$)
Wirehaired Pointing Griffons	Lau et al., 2014 ($n = 9/61$)

to conduct research on small vessel vasculitis and purulent leptomeningitis, e.g., Kawasaki disease in children and polyarteritis nodosa (Burns et al., 1991; Felsburg et al., 1992; Snyder et al., 1995; Tipold et al., 1995; Schwartz et al., 2008a; Schwartz et al., 2008b; Maiolini et al., 2012b; Spitzbarth et al., 2012; Freundt-Revilla et al., 2017). In 1991, Burns et al. provided a comparison of both diseases that show similar pathogenesis, clinical signs, and characteristic laboratory changes. The immunologic pathomechanisms, therapeutic strategies, as well as clinical monitoring could be observed and examined in dogs by frequent and feasible blood and especially CSF sampling. Furthermore, non-ethical administration of foreign material to provoke an artificial stimulation of the immune system to recreate Kawasaki-Disease in the dog as an animal model is not necessary because of the natural and spontaneous occurring inflammatory character of SRMA (Burns et al. 1991).

Etiopathogenesis

The definitive and consensual etiology leading to SRMA can still not be identified after many years of clinical, paraclinical, and immunological research (Tipold, 2000). Fig. 1 provides a visualized summary of the most important aspects of the pathogenesis of SRMA, which are explained in detailed in the following paragraphs.

Screening and searching for an infectious viral, bacterial, or parasitic agent or non-infectious environmentally toxic stimulus could not be determined as congruent etiology for SRMA (Harcourt, 1978; Meric, 1988; Scott-Moncrieff et al., 1992; Tipold and Jaggy, 1994; Tipold, 1995; Cizinauskas et al., 2000; Rose and Harcourt-Brown, 2013; Rose et al., 2014; Lazzerini, 2015; Gonçalves et al., 2021; Barber et al., 2022; Elbert et al., 2022).

In general, SRMA is understood to be an immune-mediated and non-infectious disease. This is due to a rapid clinical improvement of symptoms after administering glucocorticoids or immunosuppressive drugs and the lack of evidence of an infectious etiology (DeLahunta and Glass, 2009). Several immunologic indicators sustain and suggest the general established hypothesis of an (auto)-immune-mediated process. In association with acutely and chronically affected dogs with SRMA, the following immunologic components have been identified: antinuclear antibodies (Tipold and Jaggy, 1994), autoantibodies against central nervous system (CNS) tissue (Schulte et al., 2006), autoantibodies against intracellular components of neutrophilic granulocytes (anti--neutrophil-cytoplasmatic autoantibodies, ANCA) (Albers, 2001), exposure and production of heat shock proteins like extracellular heat shock protein 70 in the cerebrospinal fluid (CSF) (Moore et al., 2012), lupus erythematosus cells (Tipold and Jaggy, 1994), immune complex deposits (Hayes et al., 1989; Tipold and Jaggy, 1994), immunoglobulin M (IgM) rheumatoid factors (Hayes et al., 1989; Tipold and Jaggy, 1994), and vascular immunoglobulin G (IgG), immunoglobulin A (IgA) as well as IgM deposits (Tipold et al., 1995).

The pathogenesis of SRMA is mainly dominated by a Th2- and Th17-mediated humoral immune response (Schwartz et al., 2008b; Freundt-Revilla et al., 2017). The phenotype of the humoral immune response is expressed by a high $CD4^+/CD8^+$-ratio and accompanied by elevated Th2-related cytokine patterns (Tipold et al., 1999; Schwartz et al., 2008b). Interleukin-4 (IL-4) represents one of the key molecules in this humoral immune response (Schwartz et al., 2011). IL-5 and IL-10-levels were also elevated, but there was no significance detected in comparison with other inflammatory or neoplastic CNS diseases (Schwartz et al., 2011). In addition, transforming growth factor beta 1 (TGF-β_1) is upregulated intrathecally and initiates an induced humoral immune response in terms of excessive IgA synthesis (Maiolini et al., 2013).

In contrast to dominant cellular and humoral factors that are associated with a Th2-mediated immune response, the Th1-mediated immune response plays a minor role in SRMA. Th1-related cytokines and consequently the Th1-induced immune response are downregulated (Schwartz et al., 2011; Freundt-Revilla et al., 2017). IL-2 and interferon gamma (IFN-γ) are significantly downregulated and appear in low concentrations (Schwartz et al., 2011; Freundt-Revilla et al., 2017). The well-defined shift in the cytokine regulation induces a polarized and Th2-dominated immune response resulting in selective recruitment proliferation of B-lymphocytes in the peripheral blood and subarachnoid space. These B-lymphocytes produce intravascular and intrathecal IgA representing one of the hallmarks of the disease (Felsburg et al., 1992; Tipold and Jaggy, 1994; Schwartz et al., 2011; Maiolini et al., 2012a).

Th17 cells may play an important role during the immunologic dysregulation of SRMA-diseased dogs as well (Freundt-Revilla et al., 2017). The combined elevation of IL-6 and TGF-β_1 may induce the differentiation of $CD4^+$-progenitor cells to specific Th17-cells (Maiolini et al., 2013). These Th17-cells produce IL-17 during the acute phase of SRMA. Elevated IL-17 levels in serum and cerebrospinal fluid (CSF) chemotactically influence neutrophilic granulocytes and are able to harm the integrity of the blood-brain barrier (BBB) (Freundt-Revilla et al., 2017). In combination, the differentiation of Th17-cells and production of IL-17 result in one of the key events during the pathogenesis and diagnostic as well as the inflammatory hallmark of SRMA: the massive invasion of neutrophilic granulocytes in the subarachnoid space leading to severe cervical leptomeningitis (Freundt-Revilla et al., 2017).

The severe neutrophilic pleocytosis of the CSF remains one of the cardinal laboratory alterations and findings during the acute stage of SRMA (Tipold and Jaggy, 1994; Cizinauskas et al., 2000). The invasion of the subarachnoid space is explored and mediated through cellular, humoral, and chemotactic factors. On a cellular level, the adhesion integrin CD11a on neutrophilic granulocytes is upregulated, facilitating leukodiapedesis through the BBB (Schwartz et al., 2008a). Matrix-metalloproteases (MMP) 2 and 9 are selectively more highly expressed by CSF leukocytes and are able to directly damage the BBB (Schwartz et al., 2010). Finally, elevated IL-6 (Hogenesch et al., 1995; Maiolini et al., 2013) and IL-8 (Burgener et al., 1998) levels facilitate the chemotactic cross over through the BBB, resulting in characteristic neutrophilic pleocytosis or purulent leptomeningitis.

The systemic arteritis could be explained due to increased expression

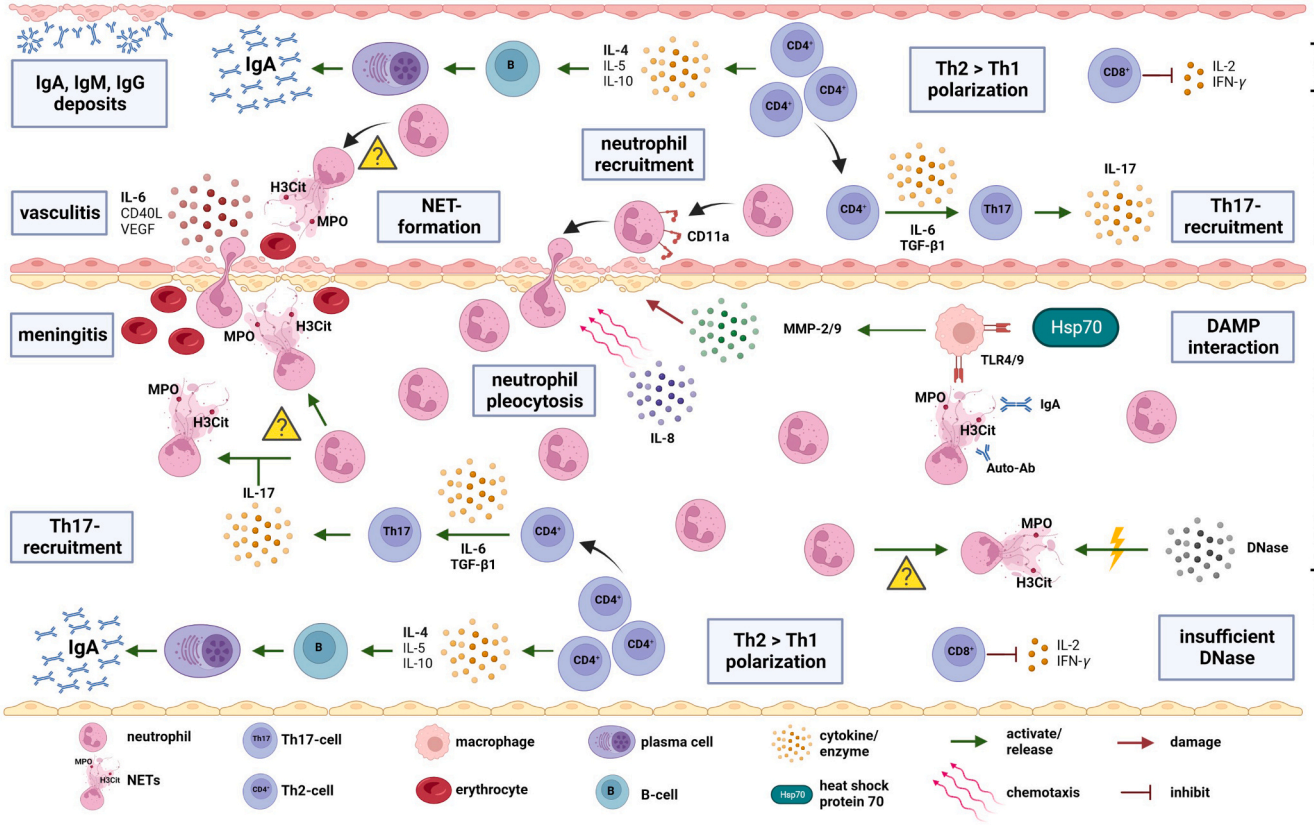

Fig. 1. Pathogenesis of steroid-responsive meningitis-arteritis (SRMA).The systemic and intrathecal humoral immune response of SRMA includes a polarized Th2 immune response, which is initiated by an increased level of Th2-related cytokines like interleukin (IL)−4, IL-5, IL-10 and decreased levels of Th1-related cytokines like IL-2 and interferon gamma (IFN-γ). The stimulation of Th2-cells results in activation and proliferation of B-cells, followed by a severe and constant production of immunoglobulin (Ig) A by plasma cells. Deposits of IgA, IgG, and IgM can be detected in the vessel walls. The other cornerstone of the humoral immune response is represented by the production of Th17-cells, induced by IL-6, and transforming growth factor beta 1 (TGF-β1) followed by IL-17 production. The pathogenesis of the severe fibrinoid-necrotizing vasculitis is not entirely understood. Increased levels of vascular endothelial growth factor (VEGF), IL-6, and CD40-ligand (CD40L) are probably responsible as well as the interaction of immunoreactive autoantigens created by neutrophil extracellular traps (NETs) like myeloperoxidase (MPO) and citrullinated Histone H3 (H3Cit). Reduced DNase activity in the CSF may enhance the impact of NETs on blood brain barrier (BBB) damage. Meningeal hemorrhage and neutrophil recruitment crossing the border of BBB is mediated due to upregulation of neutrophil integrins CD11a, intrathecal chemotactic factors like IL-8, and BBB damaging substances like matrix-metalloproteases (MMP) and interaction with autoantigens like NETs, extracellular heat shock protein 70 (eHSP70), and circulating autoantibodies.

of vascular endothelial growth factor and CD40 ligand (CD40L) during the acute phase and relapses but is not entirely understood (Maiolini et al., 2013; Freundt-Revilla et al., 2017).

The innate immune system is involved in the pathogenesis of SRMA: monocytes are observed with a higher expression of toll-like receptors (TLR) 4 and 9, possibly enhancing the inflammatory process (Maiolini et al., 2012b). These pattern recognition receptors are able to detect foreign and host-generated antigens initiating a non-specific immune response. Furthermore, an upregulation of the endocannabinoid system was described by Freundt-Revilla et al. in 2018 (Freundt-Revilla et al., 2018), that participates and modulates neuroinflammatory processes.

The latest discovery concerning the pathogenesis of SRMA is shown by the detection of neutrophil extracellular traps (NETs) in affected meninges and arteries (Wohlsein et al., 2022). The hypothesis of a dysregulated NET metabolism in SRMA is feasible due to many proinflammatory and autoantigenic stimuli that are produced in SRMA. NETs are generated as well as stimulated due to several humoral proteins like IL-17, and cellular components like the exposure of autoantigens, which were simultaneously elevated during the inflammatory process of SRMA. In addition, a significantly reduced DNase activity in the CSF could be observed that may explain an irregular NET-metabolism in dogs affected by SRMA (Wohlsein et al., 2023). NETs may connect many interactions of the cellular and humoral immune response in SRMA and serve as self-driven autoantigens in the pathogenesis of the disease (Wohlsein et al., 2022).

Beyond the unknown trigger of the immunological dysregulation, an underlying genetic cause of SRMA was determined. The small number of ancestors and the small gene pool of the Nova Scotia Duck Tolling Retriever (NSDTR) predispose this breed to genetic and hereditary diseases (Anfinsen et al., 2008). This accumulation of SRMA cases is presumably based on a genetic background or an inherited disease. Frequent occurrence of SRMA could be observed within single litters or lines. A mutual ancestor concerning the NSDTR could be detected genealogically and identified as origin of the inheritance of the disease in this specific breed (Anfinsen et al., 2008). Genealogical evidence of heritability of SRMA in NSDTRs was confirmed genetically by identifying two gene loci that were mainly involved in the development of the disease (Wilbe et al., 2009). The genetic origin of SRMA in the NSDTR is suspected and anchored at two gene loci (PP3CA and DAPP1 genes). The encoding genes ensure the activation of T-cells via the nuclear factor of activated T-cells pathway or its activator calcineurin. The mutated genes lead to increased transcription factors, which multifactorially result in pathological and excessive T-cell activity (Wilbe et al., 2009). The Th2-mediated immune response of SRMA affected dogs is dysregulated and results in excessive B-cell proliferation synthetizing excessive amounts of IgA (Felsburg et al., 1992; Tipold and Jaggy, 1994; Schwartz et al., 2008b; Schwartz et al., 2011; Maiolini et al., 2012a).

Furthermore, a clustered case of 3 littermates affected by SRMA were

described for the Petit Basset Griffon Vendéen (PBGV) (Voss et al., 2012), thus questioning the existence of inheritance within this dog breed or single litter.

Common and uncommon clinical features and localizations of SRMA

In general, clinical features of SRMA are divided up into two forms: the typical acute form and the atypical or protracted form. The clinical features mostly occur episodically and recurrently (Tipold and Schatzberg, 2010).

Veterinary practitioners and neurologists always have to consider SRMA as a systemic disease. The systemic inflammation of the disease is clinically represented by pyrexia (DeLahunta and Glass, 2009). In a retrospective study on cervical hyperaesthesia by Grapes et al. (Grapes et al., 2020), 81% of 100 dogs with SRMA showed pyrexia, and 82.6% of 350 dogs with SRMA were pyretic in a retrospective study about inflammatory diseases affecting the central nervous system by Goncalves et al. (Gonçalves et al., 2021). Both studies with large study cohorts describe that more than 80% of the affected dogs with SRMA suffer from pyrexia.

In addition to signs of a systemic inflammatory response, the acute typical form of SRMA is characterized by clinical features of leptomeningeal meningitis and arteritis of cervical and less likely by thoracolumbar spinal cord segments. The severity of the cervical or less likely thoracolumbar meningitis determines clinical signs. The disease may appear with waxing and waning character of clinical features by ameliorating or deteriorating clinical signs (Tipold and Jaggy, 1994; DeLahunta and Glass, 2009). The moderate to severe leptomeningitis results in an extremely painful cervical hyperaesthesia and less often thoracolumbar hyperaesthesia. A total of 33.6% of 298 dogs were diagnosed with SRMA, that were presented with cervical hyperaesthesia (Grapes et al., 2020). This severe cervical pain can result in a neck relieving posture called 'hunched posture' (Tipold and Schatzberg, 2010; Grapes et al., 2020). At the time of acute illness, the neurologic examination is unremarkable, with the exception of cervical hyperaesthesia due to inflammation of the cervical meninges (Tipold and Jaggy, 1994).

The atypical or protracted form occurs most probably due to inadequate immunosuppressive treatment or recurrent relapses. The inflammation of the meninges in chronic, protracted cases appears less severe than during the acute phase of the disease (Tipold and Schatzberg, 2010). The chronicity of the inflammation may cause nerve root degeneration and permanent changes of the meningeal structure due to fibrosis and mineralization of the meninges (Hoff and Vandevelde, 1981; Tipold and Jaggy, 1994; Tipold et al., 1995). These pathomorphological changes of the affected spinal cord segment result in neurological deficits like ataxia, tetraparesis or paraparesis (Tipold und Jaggy, 1994). Meningeal fibrosis rarely causes obstructions of cerebrospinal fluid flow and leads secondarily to hydrocephalus (Tipold and Jaggy, 1994). Severely thickened vessel walls may cause spinal cord compression due to chronic inflammation or haemorrhage of ruptured meningeal vessels and can be clinically detected as ataxia or paresis (Tipold and Jaggy, 1994; Zilli et al., 2021).

Besides the common clinical manifestations of SRMA displaying cervical pain or less commonly cranial nerve involvement (Tipold and Jaggy, 1994; DeLahunta and Glass, 2009), several lesions and manifestations beyond these localizations are documented. Less commonly, cranial nerve deficits such as reduced or absent menace response, anisocoria, and strabismus are observed in the chronic form of SRMA (Tipold and Jaggy, 1994; Cizinauskas et al., 2000; Lowrie et al., 2009b). These case reports are presented in the following paragraph to show the versatile appearance of SRMA in rare cases.

Abnormal optical nerve deficits have to be considered as an unusual disease manifestation in combination with other clinical features of SRMA. Tang et al. described a 9-month-old male Beagle that was presented with pyrexia (39.9 °C), neck pain, thoracolumbar hyperaesthesia, and unilateral blindness affecting the left eye (Tang et al., 2022). This case report was the first published description of an optical nerve involvement with subsequent blindness in a dog affected by SRMA.

Multifocal or intracranial neuroanatomical localized lesions caused by SRMA are very rare. Wrzosek et al. first described in a case report from 2009 cluster seizures in a 30-month-old male Boxer (Wrzosek et al., 2009). This singular case of multifocal and intracranial signs of SRMA was probably an exacerbation of a chronic recurrent case of SRMA. Excessive inflammatory reaction with pathomorphological changes of the meninges and brain parenchyma resulted in the clinical presentation of cluster seizures (Wrzosek et al., 2009).

Severe haemorrhage with consecutive extramedullary compression of the cervical spinal represents one of the major complications of SRMA (Hughes et al., 2015; Wang-Leandro et al., 2017; Zilli et al., 2021). The hemorrhage can occur in the epidural space (Zilli et al., 2021), intradural extramedullary (Wang-Leandro et al., 2017), or intradural intramedullary (Hughes et al., 2015). The condition of the individual canine patient determines treatment recommendations. Severity of the compression can lead to cardiac arrest during diagnostic imaging (Hughes et al., 2015), the need for surgical decompression (Zilli et al., 2021) or relies on long-term application of immunosuppressive or anti-inflammatory treatment given by the inflammatory nature of SRMA (Wang-Leandro et al., 2017).

Another case report in 2021 described the unusual clinical sign of severe scoliosis of a 3-year-old female-spayed German Shepherd (Poad et al., 2021). The atypical clinical sign of scoliosis was reversible and vanished after treatment with immunosuppressive drugs (Poad et al., 2021).

Other uncommon clinical features of SRMA refer to cardiac manifestation. Pathological evidence revealing arteritis of small to medium-sized cardiac arteries was first described by Snyder et al. (Snyder et al., 1995). This cardiac manifestation can result in myocarditis and is clinically documented in elevation of the cardiac biomarker Troponin I in serum samples (Snyder et al., 2010; Navarro-Cubas et al., 2011; Spence et al., 2019), electrocardiography (ECG) changes showing junctional or sinoventricular rhythm (Snyder et al., 2010), echocardiographic abnormalities presented with spontaneous echo contrast, pericardial effusion, and fractional shortening (Navarro-Cubas et al., 2011; Spence et al., 2019).

Occasionally, canine SRMA is accompanied with immune-mediated polyarthritis (IMPA) (Webb et al., 2002). Webb et al. first described a prevalence of five of 11 dogs (46%) presented with concurrent IMPA and SRMA. A recent canine study with a larger sample size reported that IMPA was simultaneously diagnosed in 31 of 350 dogs with SRMA, resulting in a prevalence of 9% (Gonçalves et al., 2021). All dogs either affected by SRMA or IMPA should be considered for joint or CSF taps in order to be given a better treatment and pain regime.

The take home message from these presented case series and reports of unusual SRMA manifestations should raise awareness of the systemic nature of this disease. Unusual disease localizations resulting in atypical clinical signs should be considered during the diagnostic process and treated in accordance with the SRMA therapy protocol.

Diagnosis

The clinical diagnosis of SRMA consists of the following findings: signalment, history, clinical features, laboratory diagnostics such as of hematology and CSF tap analysis as well as diagnostic imaging findings. A disease-specific ante-mortem biomarker is still missing.

Acute onset of cervical hyperaesthesia and clinical signs of systemic inflammation in a juvenile medium to large-sized dog in a dog breed in which SRMA is described, should add SRMA to the top of the differential diagnosis list (DeLahunta and Glass, 2009; Tipold and Schatzberg, 2010).

Typical hematologic laboratory alterations are leucocytosis with left

shift representing the systemic nature of the disease (Tipold and Jaggy, 1994; Cizinauskas et al., 2000). Furthermore, several representatives of acute phase proteins (APP) are elevated as indicators of a systemic inflammatory response. C-reactive protein (CRP) is the most commonly used APP of dogs in the diagnostic and therapy monitoring process, being a cost-efficient and minimally invasive serum biomarker (Bathen-Noethen et al., 2008; Lowrie et al., 2009a; Andersen-Ranberg et al., 2021). However, CRP is rather a non-specific biomarker and other inflammatory causes have to be ruled out during the diagnostic consideration. The clinical course of SRMA follows serum levels of CRP: decreased concentrations represent remission and increased concentrations may be the first indicator of an emerging relapse (Lowrie et al., 2009a; Andersen-Ranberg et al., 2021). A recent study by Meyerhoff et al. published in 2019 showed that the concentration of neutrophil gelatinase-associated lipocalin (NGAL) is significantly elevated in serum and CSF samples of dogs diagnosed with inflammatory central nervous system (CNS) diseases like SRMA and meningoencephalomyelitis of unknown origin (MUO) (Meyerhoff et al., 2019). The median values of NGAL in serum and CSF samples were higher in the SRMA acute group than in the group of dogs with MUO. NGAL could serve as a sufficient marker to discriminate non-inflammatory and inflammatory CNS diseases (Meyerhoff et al., 2019). An ultimate biomarker that is unique for the detection of SRMA is still not available.

CSF taps represent the crucial diagnostic tool in inflammatory CNS diseases. In SRMA, CSF samples may appear turbid, and due to subarachnoid haemorrhage, it may also appear xanthochromic or haemorrhagic (Tipold and Stein, 2010). During the initial acute phase of SRMA, CSF analysis reveals severe pleocytosis with non-degenerated neutrophilic granulocytes, increased protein content of the CSF, and a negative microbiological culture (Tipold and Jaggy, 1994; Tipold, 1995; Lowrie et al., 2009b). CSF analysis of the protracted form of the disease reveals a different inflammatory pattern. The low- to moderate-grade pleocytosis predominantly includes lymphohistiocytic cells consisting of lymphocytes as well as macrophages. The protein content of CSF shows low- to moderate-grade elevation (Tipold and Jaggy, 1994). Combined CSF taps taken from the cerebromedullar cistern and lumbar subarachnoid space may improve the diagnostic sensitivity of detecting neutrophilic pleocytosis in dogs affected by SRMA minimizing false-negative results. Especially in older dogs, a higher diagnostic yield was achieved in a study by Carletti et al. including 111 dogs (Carletti et al., 2019).

Immunoglobulin A (IgA) secretion in serum and CSF samples was previously described in SRMA-affected dogs (Felsburg et al., 1992; Tipold et al., 1994; Tipold and Jaggy, 1994; Cizinauskas et al., 2000;). Intrathecally and systemically produced IgA was measured in paired CSF and serum samples of 311 dogs with SRMA in comparison to 214 dogs with other neurologic diseases by Maiolini et al. (Maiolini et al., 2012a). Combined serologic and intrathecal IgA values are very useful for strengthen the diagnosis SRMA. However, constantly elevated IgA values in serum and CSF are regularly observed during remission so that this immunologic phenomenon diminishes IgA as a valuable monitoring and relapse indicator tool (Cizinauskas et al., 2000; Maiolini et al., 2012a).

The usage and possible value of diagnostic imaging is underrepresented in SRMA. MRI is very useful to rule out other common differential diagnoses for cervical pain (Grapes et al. 2020). MRI studies on SRMA have been very limited recently (Wrzosek et al., 2009; Tipold and Schatzberg, 2010). One retrospective study evaluated low- and high-field MRI findings in a larger study cohort including 70 dogs (Remelli et al., 2022). Nearly all dogs showed MRI abnormalities ($n = 69/70$). Most frequently, meningeal contrast enhancement (87.1%), accompanied by enhancement of the synovium of the articular facets (48.6%), or muscular contrast enhancement in the cervical region (48.6%) were detected. Furthermore, the lesions were mostly detected between the cervical level of C2 and C4 (70–75.7% of the dogs). Low- and high-field MRI studies were considered to be a useful additional diagnostic tool with concurrent CSF analysis (Remelli et al., 2022).

Treatment

Because of the immune mediated and non-infectious character of SRMA, glucocorticosteroids are the preferred immunosuppressive or anti-inflammatory drug for the treatment of SRMA (Cizinauskas et al., 2000; Tipold, 2000). Prednisolone is generally used as first-line immunosuppressive and anti-inflammatory drug of choice used for dogs with moderate to severe clinical signs and a total nucleated cell count of the CSF above 200 cells/μL (Cizinauskas et al., 2000; Lowrie et al., 2009b; Tipold and Schatzberg, 2010). Long-term administration of prednisolone for at least 6 months is recommended (Cizinauskas et al., 2000; Tipold, 2000). The following dosage scheme by Cizinauskas et al. in 2020 is generally recommended for SRMA patients for the initial prednisolone dosage loading:

- prednisolone 4 mg/kg q24h for 2 days
- prednisolone 2 mg/kg q24h for 1–2 weeks
- prednisolone 1 mg/kg q24h for 4–6 weeks

Canine patients should be evaluated with repetitive clinical, neurologic and laboratory examinations at intervals of 6–8 weeks to reduce prednisolone dosage over a period of at least 6 months. After the CSF analysis is unremarkable and blood analysis in terms of CBC and CRP are within the reference ranges, a dosage tapering of the prednisolone dosage is indicated after every examination 6–8 weeks apart (Tipold, 2000). A CSF tap is recommended 6–8 weeks after the diagnosis was made and the treatment was initiated or after every relapse. Further CSF taps are recommended if the first CSF tap after diagnosis has laboratory alterations or the dog shows any remarkable clinical signs indicating a relapse or CBC or CRP show abnormalities or treatment should be finished. The preferred dosage of prednisolone is 0.5 mg/kg q24h every 48–72 h at the end of the treatment period (Cizinauskas et al., 2000; Lowrie et al., 2009b; Tipold and Schatzberg, 2010). Excellent clinical monitoring and compliance with prednisolone administration minimizes the risk of relapse and are the keys to successful SRMA treatment.

In dogs with very mild clinical signs and a neutrophilic pleocytosis less than 200 cells/μL, non-steroidal anti-inflammatory drugs could be considered together with excellent patient monitoring (Tipold and Schatzberg, 2010). A switch to a steroidal immunosuppressive treatment is indicated and recommended, if clinical signs are deteriorating (Cizinauskas et al., 2000; Tipold and Schatzberg, 2010).

As generally known, the influence of glucocorticosteroids on the immune system is widespread and non-specific. Especially long-term administration is associated with severe side effects with gastrointestinal signs, polydipsia, polyuria, polyphagia, hair loss, weight gain, among others (Whitley and Day, 2011; Viviano, 2022). Azathioprine, ciclosporin, leflunomide, mycophenolate-mofetil or cytosine arabinoside are used as second-line or add-on therapeutic agents in combination with glucocorticosteroids to treat SRMA (Cizinauskas et al., 2000; Tipold and Schatzberg, 2010; Lau et al., 2019; Günther et al., 2020; Hilpert et al., 2020; Giraud et al., 2021; Zilli et al., 2021). The aim of using these second-line anti-inflammatory drugs in combination with glucocorticosteroids is to minimize the necessary dosage of prednisolone. Furthermore, the process of tapering the prednisolone dosage is accelerated, and the risk of severe adverse effects caused by glucocorticosteroids is decreased (Viviano, 2022).

Two retrospective studies examined the usability of azathioprine as alternative treatment options for SRMA-affected dogs (Hilpert et al., 2020; Giraud et al., 2021). In 2021, Giraud et al. investigated the combination of prednisolone and azathioprine as first-line treatment for SRMA in 26 dogs. Azathioprine was administered at a dosage of 2 mg/kg q24h for 1 month and thereafter at a dosage of 2 mg/kg every other day for another 2 months. The prednisolone dosage was initiated with 2 mg/kg q24h. After 3–5 days, the dosage was reduced to 1 mg/kg and

then tapered down every 2–4 weeks according to the individual treatment response. A total of 58% of the dogs had self-limiting side effects, that did not appreciably affect the dogs' quality of life. Only 19% of the dogs relapsed and none of the animals died or were euthanized during the treatment and follow-up (Giraud et al., 2021). In that study, prednisolone dosage was tapered down much faster than recommended in previous publications, with a very good therapeutic outcome.

In a retrospective, multi-centred study in Germany including 153 canine patients, dogs receiving monotherapy had fewer relapses than those receiving a combination of azathioprine and prednisolone (Hilpert et al., 2020). The results of that study have to be interpreted with caution, because chronic refractory cases are often associated with prednisolone resistance and a second-line immunosuppressive drug is supplemented to the treatment plan (Tipold and Schatzberg, 2010). The lack of a single azathioprine treatment group may further influence the results (Hilpert et al., 2020).

The main limitation of the presented studies is due to their retrospective nature. In future prospective studies with double-blinded study cohorts, scheduled blood as well as CSF sampling are necessary to provide valid treatment recommendations and adverse effect monitoring using second-line immunosuppressive drugs in combination with prednisolone. The waxing and waning course of SRMA and individual or self-limiting courses of the disease have to be considered in such study designs.

Another challenge for clinical neurologists is the management of relapsing and refractory cases of SRMA. Treatment protocols and recommendations for SRMA relapses are very rare and a definite consensus how to manage relapses is still missing (Cizinauskas et al., 2000; Lowrie et al., 2009b; Lau et al., 2019). A retrospective study evaluated the safety and efficacy of cytosine arabinoside on a retrospective basis in 12 dogs with relapses of SRMA (Günther et al., 2020). Cytosine arabinoside was administered after monotherapy with prednisolone, or in one single dog with prednisolone in combination with azathioprine. A total of 80% of the dogs were successfully treated with the following treatment protocol:

Every 3 weeks: Three SC administrations of cytosine arabinoside (50 mg/m^2 SC) every 12 h over 2 consecutive days or one IV administration of cytosine arabinoside (25 mg/m^2/h IV over 8 h). After this protocol is initiated, the treatment is repeated every 4, 5, and 6 weeks using the same procedure and dosage.

All dogs received prednisolone in immunosuppressive dosages immediately after a relapse. The prednisolone dosage was tapered down in accordance with the therapy protocol reported by Cizinauskas et al. (Cizinauskas et al., 2000). Major disadvantages of this treatment schedule were the high incidence of severe adverse effects, especially by additional immune-mediated diseases, including atopic dermatitis and immune-mediated thrombocytopenia, in 50% of the dogs (Günther et al., 2020). The study revealed a well-described therapy protocol for the sometimes-frustrating treatment of relapses in immune-mediated diseases like SRMA with an adequate outcome. A total of 10/12 dogs responded well to the combined immunosuppressive treatment, leading to the cautious recommendation of using cytosine arabinoside in relapsing cases of SRMA (Günther et al., 2020).

Another study performed by Cizinauskas et al. (2000) used mycophenolate-mofetil (20 mg/kg) every other day alternating with prednisolone (0.5 or 1 mg/kg) in a study population of four of the 10 dogs with refractory cases of SRMA (Cizinauskas et al., 2000). Nevertheless, larger study cohorts and prospective controlled clinical trials are desperately needed to give fundamental guidelines for SRMA relapse cases. The current treatment recommendation for dogs with SRMA including relapse cases was summarized in Table 2.

One unique case report on a 1.5-year-old mix-breed dog diagnosed with SRMA was published recently, that describes the need for medical and surgical treatment (Zilli et al., 2021). The dog was presented with acute tetraparesis, which was caused by severe epidural haemorrhage with consecutive compression of the cervical spinal cord. Decompressive surgery with a right-sided partial dorsal laminectomy of C6 was performed and followed by immunosuppressive therapy with cytosine arabinoside until wound healing was successfully terminated. Afterwards, steroids were administered (Zilli et al., 2021).

The key to adequate SRMA treatment is the increased knowledge about and greater understanding of the immunopathogenesis of SRMA. The current treatment protocols only suppress the immune system without considering specific pathways in the pathogenesis of SRMA. IgA

Table 2
Treatment recommendations for dogs diagnosed with SRMA according to previous literature research and recommendations.

Clinical condition	Medication	Dosage	Recommended duration	Ref.
Mild clinical signs + TNCC < 200 µL	Anti-inflammatory therapy with e.g., Carprofen	Carprofen: 4 mg/kg q24h or 2 mg/kg q12h	6 weeks	Tipold and Schatzberg, 2010
Moderate to severe clinical signs + TNCC > 200 µL	Immunosuppressive and anti-inflammatory medication with Prednisolone	Prednisolone: 2 – 4 mg/kg q24h 1 mg/kg q24h Tapered down to 0.5 mg/kg every 48–72 h	1 – 2 weeks 6 – 8 weeks At least 6 months	Cizinauskas et al., 2000 Tipold, 2000 Tipold and Schatzberg, 2010
Relapse	Immunosuppressive and anti-inflammatory medication with Prednisolone and second-line immunosuppressive drug	Prednisolone: 2 – 4 mg/kg q24h 1 mg/kg q24h tapered down to 0.5 mg/kg every 48–72 h In combination with	1 week 2 – 4 weeks At least 6 months In combination with	Cizinauskas et al., 2000 Tipold, 2000 Tipold and Schatzberg, 2010
	Azathioprine	Azathioprine: 2 mg/kg q24h 2 mg/kg every 48 h	1 month 2 months	Tipold and Schatzberg, 2010 Hilpert et al., 2020 Giraud et al., 2021
	Cytosine arabinoside	Cytosine arabinoside: 3 × 50 mg/m^2 s.c. over 2 days or 25 mg/m^2/h IV over 8 h	every 3, 4, 5, 6 weeks or every 3, 4, 5, 6 weeks	Günther et al., 2020
	Mycophenolate-mofetil	20 mg/kg q24h every other day alternating with prednisolone	At least 6 months	Cizinauskas et al., 2000

TNCC, total nucleated cell count in cerebrospinal fluid.

production still remains high even under the described immunosuppression, thus indicating the ongoing nature of the disease (Cizinauskas et al., 2000; Maiolini et al., 2012a). IL pathways represent crucial therapeutic targets for a specific immunotherapy (Tipold et al., 1995; Hogenesch et al., 1995; Burgener et al., 1998; Spitzbarth et al., 2012; Maiolini et al., 2013; Freundt-Revilla et al., 2017; Andersen-Ranberg et al., 2021). Furthermore, the role and influence of NETs and their metabolism in the pathogenesis of SRMA could serve as promising therapeutic targets in the future (Wohlsein et al., 2022). On the other hand, prospective, double-blinded clinical trials are necessary to launch new specific immunosuppressive agents.

Prognosis

The prognosis for dogs is fair to good for those receiving an immediate diagnostic work-up, with the animals responding excellently to subsequent immunosuppressive therapy (Tipold and Schatzberg, 2010). Chronic and protracted clinical courses with recurring relapses occur due to inconsistent administering of or resistance to the glucocorticosteroid monotherapy and are provided with a guarded prognosis (Cizinauskas et al., 2000; Tipold and Jaggy, 1994; Tipold and Schatzberg, 2010). Breed differences are described for the clinical outcome. According to Behr and Cautinille in 2006, the prognosis for Boxers is much better than for Beagles and Bernese Mountain dogs (Behr and Cauzinille, 2006; Presthus, 1991; Snyder et al., 1995).

Relapse rates are described with a range from 16% to 60% depending on the respective study: 16% (Bathen-Noethen et al., 2008), 19% (Giraud et al., 2021), 20% (Lowrie et al., 2009b), 25% (Tipold and Jaggy, 1994), 29.4% (Hilpert et al., 2020), 32.4% (Biedermann et al., 2016), 48% (Lau et al., 2019), and 60% (Cizinauskas et al., 2000).

The mortality rate of SRMA ranges from 4.6% to 8.1%. These values underline the generally good prognosis of the disease and reinforce that individual dogs are euthanized only in rare cases due to therapy-resistant, recurrent relapses severe intradural haemorrhage, or massive complications of immunosuppressive medication (Tipold and Jaggy, 1994; Hughes et al., 2015; Biedermann et al., 2016; Hilpert et al., 2020).

Conclusions

In future, studies should include prospective treatment trials evaluating and creating treatment recommendations and establishes consensual guidelines. Pilot studies using specific immunosuppressive drugs like monoclonal antibodies diminishing IL-17-dependent responses or recombinant DNases combating NET-metabolism need an introduction in veterinary medicine and especially in inflammatory diseases affecting the central nervous system. Specific genetic research into dog breeds commonly diagnosed with SRMA is necessary to promote breeding schemes.

Declaration of Competing Interest

None of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

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