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REVIEW ARTICLE

Sudden acquired retinal degeneration syndrome (SARDS) – a review and proposed strategies toward a better understanding of pathogenesis, early diagnosis, and therapy

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Abstract

Sudden acquired retinal degeneration syndrome (SARDS) is one of the leading causes of currently incurable canine vision loss diagnosed by veterinary ophthalmologists. The disease is characterized by acute onset of blindness due to loss of photoreceptor function, extinguished electroretinogram with an initially normal appearing ocular fundus, and mydriatic pupils which are slowly responsive to bright white light, unresponsive to red, but responsive to blue light stimulation. In addition to blindness, the majority of affected dogs also show systemic abnormalities suggestive of hyperadrenocorticism, such as polyphagia with resulting obesity, polyuria, polydipsia, and a subclinical hepatopathy. The pathogenesis of SARDS is unknown, but neuroendocrine autoimmune mechanisms have been suggested. Therapies that target these disease pathways have been proposed to reverse or prevent further vision loss in SARDS-affected dogs, but these treatments are controversial. In November 2014, the American College of Veterinary Ophthalmologists’ Vision for Animals Foundation organized and funded a Think Tank to review the current knowledge and recently proposed ideas about disease mechanisms and treatment of SARDS. These panel discussions resulted in recommendations for future research strategies toward a better understanding of pathogenesis, early diagnosis, and potential therapy for this condition.

Key Words: autoimmune retinopathy, blindness, canine, endocrinopathy, hyperadrenocorticism, sudden acquired retinal degeneration syndrome

INTRODUCTION

In 2013, the American College of Veterinary Ophthalmologists’ Vision for Animals Foundation (ACVO-VAF) surveyed the ACVO membership by e-mail about the ophthalmic disorders where focused research funding and efforts would probably result in significant improvements in the diagnostic and therapeutic management of animal patients. Very clearly, supported by 83% of the respondents, sudden acquired retinal degeneration syndrome (SARDS) was the most commonly reported condition requiring further investigation. Subsequently, the VAF Board of Directors organized and funded a Think Tank of clinicians and basic scientists to develop recommendations...
for future research strategies that will enhance our knowledge and help improve early diagnosis and treatment of SARDS. On November 14, 2014 members of the Think Tank held a 1-day meeting at the Westin Hotel, Detroit Metropolitan Airport in Michigan (USA). This article is a comprehensive review of the current literature on SARDS (Table 1) and a summary of the Think Tank’s recommendations.

WHAT IS SARDS?

The first formal reports of SARDS emerged in the United States in the early 1980s, when the condition was also referred to as ‘toxic metabolic retinopathy’ and ‘silent retina syndrome’.1–5 The syndrome has also been described in other parts of the world.6–8 Based on our observations, we suspect that SARDS has become a leading cause of currently incurable vision loss in dogs. When first confronted with a diagnosis of SARDS, most pet owners tend to be devastated by the news of irreversible blindness in their dogs, and many are desperate to seek treatment to help the animal’s condition. The acute loss of sight, which is frequently combined with systemic abnormalities and age-related health issues, often results in deteriorated quality of life for the dog and owner, at least during the initial adjustment period.9–11 Affected dogs tend to be more cautious, less playful, and more lethargic.11

SARDS typically affects middle-aged to elderly and often moderately overweight dogs.3,5,11–13 The reported mean or median ages of affected dogs range from 7 to 10 years.3–5,11–18 Between 60 and 90% of affected dogs are female; the majority of them are spayed.3,5,11–17 A genetic predisposition for SARDS has not been documented and any breed can be affected, with the disease diagnosed most commonly in mixed-breed dogs. However, small breeds including the dachshund, miniature schnauzer, pug, Brittany, bichon frisé, beagle, Maltese, American cocker spaniel, Pomeranian, and possibly shih tzu are reported to be most commonly affected.5,8,11–21

Typically, dogs affected with SARDS are presented for assessment of rapid vision loss that develops over a period of days to weeks.1–5,11,14,16 Histology of a limited number of affected eyes showed a loss of photoreceptor outer segments, resulting in an extinguished electroretinogram (ERG), which, when seen in conjunction with a clinically normal appearing fundus, is considered the hallmark of SARDS and allows differentiation from other, neurologic causes of acute vision loss, such as optic neuritis and intracranial neoplasia, where the ERG is generally not affected.1–5,14,19,20,22–26 Typically, patients with SARDS do not show obvious neurologic signs; however, in our experience, some exhibit agitation potentially due to acute vision loss or related to systemic involvement. Initially, ophthalmic examination findings are normal or insufficient to explain the degree of visual impairment. Specifically, the ocular fundus appears normal or is affected by subtle degenerative or vascular changes inconsistent with the magnitude of visual impairment.1–7 More obvious ophthalmoscopic signs indicative of generalized retinal degeneration/atrophy, such as a hyper-reflective tapetal fundus (resulting from retinal thinning), attenuation of the retinal vasculature, and pallor of the optic nerve head, are typically seen several months after the onset of SARDS.1–5,27

In the majority (~90%) of SARDS-affected dogs the pupils are mydriatic with diminished response to bright white light.1–5,27,28 This aspect of the disease phenotype has been explored in more detail over the last few years by Grozdanic et al.28 and resulted in the recommendation that chromatic pupillary light reflexes (PLRs) may serve as a practical diagnostic tool to assess the canine visual pathways. In addition to electroretinography, loss of photoreceptor function can be verified clinically by observation of the lack of a PLR following stimulation with a bright (200 kcd/m²) red light of 630 nm wavelength which primarily stimulates the cone photoreceptors.28–32 Because retinal ganglion cells (RGCs), including the melanopsin-expressing intrinsically photosensitive RGCs (ipRGCs),33–35 are initially not affected by SARDS, PLRs are retained when eyes are stimulated with a bright (200 kcd/m²) blue light of 480 nm wavelength that corresponds to the peak spectral sensitivity of melanopsin.27,28 whereas red light with a wavelength of 630 nm does not overlap with the melanopsin absorption spectrum.28,34,35 Chromatic PLR testing is easily performed, can be performed on an unanesthetized animal, and complements electroretinography in the diagnosis of SARDS.21,27,28

Light and electron microscopic examination has been performed in only a few SARDS-affected eyes and has shown that, in eyes examined within 3 weeks following the onset of blindness, pathology is limited to the rod and cone photoreceptors manifest as extensive panretinal loss of photoreceptor outer segments.3,4,20,25,26 Subsequently, photoreceptor inner segments are also shortened, followed by apoptosis of rods and cones, leading to thinning of the outer nuclear layer.1,3,4,19,25,26 Slow degeneration of the inner retina, including bipolar, amacrine, and ganglion cells, follows loss of rods and cones and occurs over several months to years.3,4,26 All retinal regions appear to be equally affected, although central retinal cells may be lost more gradually than those in the peripheral retina.3,4,26 While inflammation is not considered an important feature of SARDS, variable numbers of macrophages were found in the interphotoreceptor matrix.4,20 The presence of intraretinal antibody-producing plasma cells has also been proposed.27

Even with increasing availability in veterinary ophthalmology,16 optical coherence tomography (OCT) has not yet been performed on a sufficiently large number of patients with SARDS to permit firm conclusions; however, preliminary reports describe initial thinning of the nerve fiber layer and total retinal thickness, especially in the inferior retina.27,37,38

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Table 1. Summary of publications regarding sudden acquired retinal degeneration syndrome (SARDS)

<table>
<thead>
<tr>
<th>Publication</th>
<th>Number of SARDS cases</th>
<th>Investigations used</th>
<th>Peer review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vainisi et al.</td>
<td>18</td>
<td>Clinical exam, serum biochemistry, protein and lipids, endocrinologic assessment, vitamins and selenium, ERG, FA, tests for autoimmune disease</td>
<td>N*</td>
</tr>
<tr>
<td>Acland et al.</td>
<td>26</td>
<td>Clinical exam, obstacle course, CBC, serum biochemistry, lead levels, urinalysis (incl. amino acids), endocrinologic assessment, CSF analysis, ERG, FA, necropsy, light and electron microscopic examination of the retina</td>
<td>N*</td>
</tr>
<tr>
<td>Bellhorn et al.</td>
<td>5</td>
<td>Circulating AAbs (ELISA, Western blot, complement fixation assay)</td>
<td>Y</td>
</tr>
<tr>
<td>Riis</td>
<td>1</td>
<td>Light and electron microscopic examination of the retina</td>
<td>N*</td>
</tr>
<tr>
<td>Van der Woerd et al.</td>
<td>36</td>
<td>Clinical exam, ERG, CBC, serum biochemistry, urinalysis, endocrinologic assessment, immunoglobulins, light and electron microscopic examination of the retina, ultrasonography (adrenal gland and liver), CT (brain/pituitary and adrenal gland), liver biopsy, CSF analysis</td>
<td>Y</td>
</tr>
<tr>
<td>O’Toole et al.</td>
<td>2</td>
<td>Clinical exam, ERG, CBC, serum biochemistry, urinalysis, fecal examination, thoracic and abdominal radiographs, endocrinologic assessment, ultrasonography (adrenal gland and liver), CT (brain/pituitary and adrenal gland), liver biopsy, CSF analysis</td>
<td>Y</td>
</tr>
<tr>
<td>Mattson et al.</td>
<td>1</td>
<td>Clinical exam, ERG, CBC, serum biochemistry, urinalysis, fecal examination, thoracic and abdominal radiographs, endocrinologic assessment, ultrasonography (adrenal gland and liver), CT (brain/pituitary and adrenal gland), liver biopsy, CSF analysis</td>
<td>Y</td>
</tr>
<tr>
<td>Miller et al.</td>
<td>3</td>
<td>Clinical exam, ERG, serum biochemistry, endocrinologic assessment, light microscopic examination of the retina, incl. TUNEL</td>
<td>Y</td>
</tr>
<tr>
<td>Holt et al.</td>
<td>38</td>
<td>Clinical exam, ERG, serum biochemistry, urinalysis, endocrinologic assessment</td>
<td>N*</td>
</tr>
<tr>
<td>Abrams et al.</td>
<td>12</td>
<td>Surveys completed by dog owners and veterinary ophthalmologists</td>
<td>N*</td>
</tr>
<tr>
<td>Van der Linden et al.</td>
<td>24</td>
<td>Questionnaires for dog owners to assess quality of life</td>
<td>N*</td>
</tr>
<tr>
<td>Gilmour</td>
<td>18</td>
<td>Clinical exam, ERG CBC, serum biochemistry, thoracic radiography, ultrasonography (adrenal glands), CT (brain, pituitary gland), survey for dog owners to assess quality of life</td>
<td>N*</td>
</tr>
<tr>
<td>Levin</td>
<td>4</td>
<td>Endocrinologic assessment and therapy</td>
<td>N*</td>
</tr>
<tr>
<td>Gilmour et al.</td>
<td>17</td>
<td>Clinical exam, ERG CBC, serum biochemistry, thoracic radiography, ultrasonography of adrenal glands, CT of pituitary glands, circulating AAbs (Western blot)</td>
<td>Y</td>
</tr>
<tr>
<td>Keller et al.</td>
<td>13</td>
<td>Clinical exam, ERG, circulating AAbs (Western blot and ELISA)</td>
<td>Y</td>
</tr>
<tr>
<td>Braus et al.</td>
<td>24</td>
<td>Clinical exam, ERG, circulating AAbs (Western blot, ELISA)</td>
<td>Y</td>
</tr>
<tr>
<td>Grozdanic et al.</td>
<td>5</td>
<td>Clinical exam, ERG, chromatic pupillometry</td>
<td>Y</td>
</tr>
<tr>
<td>Grozdanic et al.</td>
<td>19</td>
<td>Clinical exam, ERG, chromatic PLR, OCT of retina, light microscopic examination of the retina, incl. IHC</td>
<td>N</td>
</tr>
<tr>
<td>Grozdanic et al.</td>
<td>12</td>
<td>Clinical exam, ERG, chromatic PLR, OCT of retina, behavioral vision testing, retinal microarray, light microscopic examination of the retina, incl. IHC</td>
<td>N*</td>
</tr>
<tr>
<td>Montgomery et al.</td>
<td>120</td>
<td>Clinical exam, ERG, CBC, serum biochemistry, urinalysis, serological testing for Lyme disease, MRI of brain, CSF analysis</td>
<td>Y</td>
</tr>
<tr>
<td>Carter et al.</td>
<td>13</td>
<td>Clinical exam, ERG, CBC, serum biochemistry, urinalysis, endocrinologic evaluation, blood pressure</td>
<td>Y</td>
</tr>
<tr>
<td>Stuckey et al.</td>
<td>100</td>
<td>Clinical exam, ERG, questionnaire completed by dog owners</td>
<td>Y</td>
</tr>
<tr>
<td>Heller et al.</td>
<td>495</td>
<td>Clinical exam, ERG, effect of breed and body weight</td>
<td>N</td>
</tr>
</tbody>
</table>

*Conference abstracts.

AAbs, antiretinal antibodies; CBC, complete blood count; CSF, cerebrospinal fluid; CT, computed tomography; ELISA, enzyme-linked immunosorbent assay; ERG, electroretinogram; FA, fluorescein angiogram; IHC, immunohistochemistry; OCT, optical coherence tomography; MRI, magnetic resonance imaging; PLR, pupillary light reflex; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling.

Despite investigations performed over more than three decades, etiopathogenic aspects of SARDS are still not understood and remain quite controversial. In part, the absence of knowledge and consensus regarding these critical features relates to lack of peer-reviewed investigations, but knowledge and consensus is also hampered by controversy about whether the SARDS diagnosis is being used to describe diseases of multiple different etiopathogeneses. For example, although the acronym itself and initial reports describe a sudden onset of vision loss, some owners report that weight gain, polyphagia (PP), polyuria (PU), polydipsia (PD), and sometimes evidence of suspected visual deficits were present weeks or months before acute, complete vision loss. This may represent a separate disease phenotype or an early more gradual manifestation of ‘classic’ SARDS. Likewise, variable presence of coincident systemic signs has also led to some confusion regarding etiologic classification systems. As many as 85% of SARDS-affected dogs are presented with systemic clinical signs, and up to 75% of SARDS-affected dogs have laboratory abnormalities consistent with those seen in certain endocrinopathies. These systemic signs may precede vision loss or occur at approximately the same time. Although PP can increase in severity for at least 1 year following the diagnosis of SARDS, in many dogs systemic signs decrease over months leaving only blindness as the remaining clinical sign. It is not known how these systemic signs may be linked to photo-
receptor loss and acute blindness or whether, when present, they represent a variant of SARDS. Loss of olfaction is also reported in some SARDS-affected dogs, resulting in difficulty detecting food even when it is in close proximity to their noses; however, it is not known how loss of olfaction is possibly linked to the retinal disease.

Causation also remains undetermined despite numerous epidemiological studies suggesting some correlative risk factors. For example, some authors have suggested a seasonality of disease incidence, with peaks in December and January in the northeastern United States. However, this winter peak is not supported by studies from other geographic regions. Dogs from rural or urban environments can be affected by SARDS, and no environmental risk factors have been identified so far. However, concerns have been raised on internet sites and e-mail discussion groups that SARDS could be triggered by stressful situations, such as general anesthesia, grooming appointments, kennel stays, household changes, use of certain antiparasiticides, or vaccination. Glutamate excitotoxicity has also been proposed as a possible mechanism of photoreceptor death in SARDS. Increased glutamate concentrations were reported in vitreous samples collected from SARDS-affected dogs. However, since the vitreous samples were submitted for amino acid analysis within the laboratory of E. Dreyer at Harvard Medical School and this researcher was later convicted of scientific misconduct by the United States Department of Health and Human Services, the integrity of analyses on these samples should be questioned (grants.nih.gov/grants/guide/notice-files/NOT-OD-01-006.html).

Taken together, this wide variation in syndromic signs and the lack of proven causation have led to much controversy regarding etiopathogenesis and whether SARDS is a single disease entity. This has also led some to assign diagnostic ‘labels’ originally used for human conditions such as immune-mediated retinitis (IMR), autoimmune retinopathy (AIR), and cancer-associated retinopathy (CAR) to various clinical presentations in dogs. These are discussed more fully below. It remains unclear whether the conditions seen in dogs are sufficiently similar to those described in humans to permit such diagnoses. Regardless of cause, SARDS remains a devastating diagnosis with up to one quarter of SARDS-affected dogs being euthanized as a result of real or perceived deterioration in quality of life due to some combination of acute, complete vision loss, associated systemic abnormalities, or other age-related health issues.

ENDOCRINOPATHIES ASSOCIATED WITH SARDS

In a majority of SARDS-affected dogs, vision loss is seen in conjunction with systemic signs (PP, PU, PD, weight gain, apparent anxiety, panting, etc.) and/or laboratory abnormalities (lymphopenia, neutrophilia, elevated serum alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), or cholesterol, as well as reduced urine specific gravity and/or proteinuria) consistent with those seen in certain endocrinopathies such as hyperadrenocorticosis. Recent work has also assessed changes in circulating sex hormone concentrations. Carter et al. reported that over 90% of SARDS-affected dogs have elevated adrenal sex hormone and/or cortisol serum concentrations, before and/or after stimulation with adrenocorticotropic hormone (ACTH). The sex hormones most commonly elevated are 17-hydroxyprogesterone and progesterone, followed by estradiol, androstenedione, and rarely testosterone. These sex hormones can exhibit glucocorticoid-like activity. For example, 17-hydroxyprogesterone and progesterone are major precursors to the production of cortisol and androgens in the steroid pathway. It is possible that elevated steroid hormones trigger photoreceptor apoptosis in SARDS-affected dogs. Similarly, pre-ACTH stimulation cortisol levels have been inversely correlated with visual function as measured by ERG, and SARDS-affected dogs have altered blood flow in the ophthalmic artery and vein as measured by Doppler ultrasonography. Carter et al. suspected pituitary abnormalities in the majority of their patients with SARDS based on the normal to high circulating ACTH values, which were considered inappropriate combined with the documented adrenal hyperactivity. In addition to abnormal ACTH response test, ~60% of SARDS-affected dogs may also have abnormal results from a dexamethasone suppression test. Therefore, it has been recommended that dogs with SARDS and clinical signs suggestive of hyperadrenocorticosis should be further evaluated, using techniques such as pituitary and adrenal gland imaging. Despite indications of adrenal cortical hypersecretion, only about 20% of SARDS-affected dogs are diagnosed with typical hyperadrenocorticism, and unlike Cushing’s syndrome in dogs, the systemic signs in dogs with SARDS without typical hyperadrenocorticosis often resolve (although the blindness does not). Also, despite hyperadrenocorticism being relatively prevalent in middle-aged to older dogs, we are aware of only two reports documenting development of SARDS in dogs with confirmed preexisting hyperadrenocorticism. Thus, a causal relationship between SARDS and hyperadrenocorticism remains controversial.

Others have suggested that the atypical hyperadrenocorticism seen in patients with SARDS represents a physiologic response to stress such as sudden vision loss. However, similar signs are not seen in patients with other diseases causing apparently rapid onset of vision loss, such as optic neuritis, and to the authors’ knowledge, a comparable syndrome has not been described in other species including humans. Finally, some have claimed that, because the initially elevated serum cortisol concentrations in patients with SARDS
subsequently decline, and are accompanied by increased adrenal sex hormone concentrations and subnormal thyroid concentrations, this may represent a form of 'adrenal gland exhaustion'. Therefore they have recommended the term 'atypical cortisol estrogen imbalance syndrome' or the eponymous 'Plechner’s syndrome' for this condition (drplechner.com). As a result, glucocorticoid and thyroid hormone replacement therapy for patients with SARDS by these authors following detailed serum cortisol and adrenal sex hormone measurements. However, there are no controlled, peer-reviewed studies supporting successful treatment outcomes.

The systemic clinical signs and loss of olfaction noted in many patients with SARDS may also be suggestive of a neuroendocrine disorder. The olfactory bulb houses dopamine neurons, which are known to be involved in the regulation of olfactory function. The role of dopamine neurons in the olfactory bulb in SARDS-induced loss of olfaction has not been explored. The retina is home to the dopaminergic system whose function still remains unclear. Whether there is any relationship between the loss of olfaction noted in SARDS to any possible changes observed in dopaminergic neurons in the retina has not been investigated. A similar relationship between dopaminergic systems in the olfactory bulb and the nigrostriatal dopamine neurons in Parkinson’s disease has been explored.

**IS SARDS A FORM OF AUTOIMMUNE RETINOpatHY?**

Autoimmunity as a potential etiology for SARDS has been investigated many times over the last 30 years. Recently, there have been claims of prevention or reversal of vision loss following aggressive immunosuppressive therapy. However, these claims remain controversial because they have not yet undergone peer review or been repeated by other clinicians. The failure of patients with SARDS to reliably respond to immunosuppressive therapies that are typically effective for other autoimmune diseases fails to support the purported autoimmune pathogenesis. The following paragraphs provide a comprehensive review of human AIR with an emphasis on investigations that are urgently needed to assess the role of autoimmunity in canine SARDS.

Similar to SARDS, many forms of AIR in humans are characterized by an unexplained sudden (typically within weeks to months) and progressive loss of vision with minimal change in the appearance of the ocular fundus in the early stages, severe attenuation or loss of ERG amplitudes, apoptosis of photoreceptors, and lack of intraocular inflammation. Comparable to SARDS, AIR occurs twice as commonly in females as it does in males, and the disease is typically diagnosed in middle-aged individuals between the ages of 50 and 70 years. About 60–70% of patients with AIR have a family history of other autoimmune disorders, such as rheumatoid arthritis, lupus, thyroid disease, or asthma. The condition presents either as the primary autoimmune condition *non-paraneoplastic AIR (npAIR)* or associated with various forms of nonocular neoplasia where it is defined as either cancer-associated retinopathy (CAR) or melanoma-associated retinopathy (MAR). Because concurrent cancer cannot always be diagnosed at the time AIR is diagnosed, a diagnosis of npAIR may subsequently be converted to CAR or MAR. Alternatively, cancer may be diagnosed months to years prior to AIR. A connection between SARDS and cancer has been ruled out in dogs; however, this notion has recently been challenged by Grozdanic and colleagues.

Because the ocular fundus of patients with AIR tends to appear fairly unremarkable, the use of additional diagnostic tools is needed. In addition to visual field deficits, which cannot be easily determined in dogs, severely decreased ERG amplitudes are also often observed in human patients with AIR. The result is an autoimmune reaction against retinal proteins, resulting in retinal dysfunction and cell death through activation of apoptosis. Serum antibody analysis is typically performed by a combination of Western blot, immunohistochemistry (IHC), and enzyme-linked immunosorbent assay (ELISA). For the Western blot technique, proteins extracted from a normal retina are separated into discrete bands according to their molecular weight by gel electrophoresis and then transferred to a membrane that is subsequently incubated with the patient’s serum. A tagged secondary antibody (anti-human or anti-dog immunoglobulin depending on the patient species being tested) binds and marks any of the patient’s AAbs bound to the retinal proteins on the membrane. For IHC, histologic sections of normal retina are incubated with the patient’s serum and any antibodies binding to the retina will be identified, as for Western blot, with tagged secondary antibodies. This technique allows identification of the specific retinal cells being targeted by the AAbs. The principles of ELISA are very similar to those of IHC and Western blot analy-

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sis: small wells are coated with specific retinal proteins and then incubated with the patient's serum. Any AAbs bound to the retinal protein in the well will be detected with a tagged secondary antibody and a colorimetric reaction which is measured with a spectrophotometer. The ELISA technique allows measurement of titers by testing serially diluted serum samples. Titers of relevant AAbs are higher in patients with AIR compared to normal controls, and a decrease in titer in response to therapy is sometimes considered clinically relevant.

The interpretation of serum antibody analysis can be quite difficult, mostly because AAbs can also be found at some level in over half of normal humans and are therefore not always pathogenic or clinically relevant. Thus, mere presence of AAbs in an individual's serum is insufficient to establish a diagnosis of AIR. Typically, more proteins are targeted by AAbs, and the staining intensity stronger when comparing Western blots of AIR patients with normal controls. Since many AAbs are benign, it has to be verified that identified AAbs are truly pathogenic, for example, by intravitreal injection into a normal animal. Only a few of the many AAbs found in patients with AIR have been proven to cause retinal degeneration, and the clinical manifestation can vary depending on the retinal protein and cell type targeted.

Antibodies directed against multiple specific retinal antigens have been identified in patients' sera; only antirecoverin and anti-α-enolase will be discussed in detail here. These two AAbs have been most frequently found in patients with AIR (both npAIR and CAR) and induce apoptosis of photoreceptors, bipolar cells, and retinal ganglion cells. If anti-α-enolase AAbs are not typically found in the normal population and, when present in healthy individuals, usually target different epitopes and do not induce apoptosis. Recoverin is primarily expressed in photoreceptors where it plays a regulatory role in phototransduction. However, it can also be aberrantly expressed by tumors of patients with CAR, suggesting that antibodies formed against the tumor's recoverin cross-react with photoreceptors.

Enolase is a ubiquitously expressed glycolytic enzyme with three isoforms: α-enolase, found in many tissues; β-enolase, found predominantly in muscle; and γ- or neuron-specific enolase (NSE), found in neurons, neuroendocrine tissues, and photoreceptors. Antibodies against NSE, not anti-α-enolase antibodies as in human patients with AIR, were found in six of 24 dogs studied with SARDS, whereas none of the normal control dogs tested had detectable NSE autoantibodies. This finding represents the strongest indication to date of an autoimmune pathogenesis for at least some cases of SARDS. Other studies have also documented AAbs in SARDS-affected dogs, but their results were not conclusive.

Therefore, a clear relationship between the presence of serum AAbs and the development of retinal disease still needs to be established for SARDS. Based on the lessons learned from human AIR studies, a similar autoimmune pathogenesis in SARDS cannot be ruled out simply because AAbs were not found in some affected dogs or were also found in normal control dogs.

Similar to SARDS, AIR is not associated with any clinical signs of intraocular inflammation. Except for a few macrophages in the regions of retinal cell loss, no significant inflammation is seen histologically within AIR-affected retinas. However, T and B lymphocytes probably contribute to the disease process as suggested by documented activation of the complement system. This is further supported by the recent IHC detection of immunoglobulin-rich plasma cells, T lymphocytes, and activated microglia embedded within the SARDS-affected retina and an increase in expression of genes associated with antigen presentation, immunoglobulin synthesis, complement, apoptosis, and pro-inflammatory mediators by microarray analysis. This resulted in the novel proposition of intraretinal AAbs production. Our review of the literature on SARDS and AIR confirms that the potential role of cellular autoimmunity urgently requires investigation.

Several treatment strategies are used in patients with AIR, including steroids, intravenous immunoglobulins (IVIg), immunosuppressive drugs, such as cyclosporine, azathioprine, mycophenolate mofetil, and cytolytic antibodies, such as rituximab and alemtuzumab that target specific lymphocyte subpopulations. Long-term immunosuppressive treatment for at least 3–4 months is needed to achieve a therapeutic effect; however, treatment is not always effective, especially when there is already severe loss of retinal cells. If treatment is effective, it may need to be continued for years in order to prevent recurrence. Disease parameters routinely screened to assess treatment outcome include visual function, ERG amplitudes, and AAbs titer. Assuming SARDS and especially the proposed early phenotype – IMR – are autoimmune diseases, Grozdanic and colleagues began immunosuppressive therapy using high doses of systemic steroids, intravenous or intraocular administration of human IVIg, and systemic immunosuppressive therapy, such as cyclophosphamide and cyclosporine in some affected dogs. They described positive treatment outcomes in a number of dogs, but these remain controversial due to the lack of peer-reviewed reports and because others have not replicated their work.

RECOMMENDATIONS FROM THE THINK TANK REGARDING REQUIRED RESEARCH

Because the pathogenesis of SARDS remains poorly understood and no effective treatments exist, Think Tank
members believe that research strategies and data collection remain essential. Since the term SARDS has been applied more widely in recent years than the original definition was, well-defined inclusion and exclusion criteria for patients with SARDS will be critical in future studies. There is also a clear need for the identification and examination of SARDS-affected dogs in the acute phase of disease in order for studies of pathogenesis and etiology to be more accurate and therapeutic strategies to be more effective. We recommend that all studies must include carefully selected normal control dogs, ideally breed, age, and sex matched, from a similar environment, and available for extensive examinations and sample collection. There would be advantages from establishing a national or international center for data and sample collection and long-term storage. Existing databases that could serve as templates are the Immune Tolerance Network (www.immunetolerance.org) or the canine eye database maintained by the Orthopedic Foundation for Animals (www.ofa.org). This approach would support multicenter studies and more efficient collection of larger number of samples and data that are uniformly handled and stored with the necessary quality control. Although difficult and costly, we recommend longitudinal monitoring of potential SARDS biomarkers as performed in larger human epidemiologic studies, such as the Beaver Dam Eye Study (www.bdeye-study.org). This may enable identification of early disease parameters, thereby permitting earlier SARDS diagnosis and initiation of therapy prior to photoreceptor death.

Based on proposed disease mechanisms discussed herein, serum and/or plasma should be collected for detection and characterization of AAbs, hormones, and cytokines, as well as whole blood for DNA and lymphocyte isolation. Other potentially useful samples for similar assessments include aqueous and vitreous humor; however, collection of these is more invasive and less practical. Given the diversity of assays and lability of some parameters assessed, sample collection, handling, and storage would require careful planning. Detailed histologic and molecular evaluation of tissue samples is also a high priority; however, because dogs tend to live several years following diagnosis of SARDS, and because affected eyes do not need to be enucleated, access to tissues is limited. Access to appropriate control tissues is similarly difficult. Sponsored tissue donation and public awareness programs would be very useful. Until then, evaluation of archival tissue samples will be important. Strong evidence that dysregulated immune interactions with commensal intestinal microbiota play a role in generation of autoimmunity led the panel to also consider collection and storage of gastrointestinal flora, including fecal samples, for future evaluation of the microbiome of affected and normal animals. As a general consideration for future studies, investigators are encouraged to widen the range of possible etiologies to include nutritional, toxic, and infectious causes.

We recognize that some proposed strategies are ambitious and costly and cannot be realistically performed at many institutions and that funding for canine-specific conditions also is limited. However, the ACVO-VAF is dedicated to provide initial funds through a special grant application process. If investigations reveal similar disease mechanisms in SARDS and human diseases such as AIR, additional funding options for translational research may become available through agencies such as the National Institutes of Health. As a guide for future studies, the remaining paragraphs contain recommended outcome measures and minimal databases that should be collected from SARDS-affected and control animals.

**Clinical examination**
A thorough clinical history, systemic and ophthalmic examinations, and standardized data collection and sample storage methods for SARDS-affected and control animals are essential for disease characterization. For identification of genetic and environmental risk factors, historical data should be collected using a detailed standardized questionnaire that includes questions about recent potentially stressful events, medications, occurrence of PU, PD, PP, and weight gain, etc. Signalment data must include age, sex, neuter status, breed, body weight, and body condition score. Ophthalmic evaluation must include slit-lamp biomicroscopy, ophthalmoscopy, digital fundus photography, chromatic PLR assessment, tonometry, standardized behavioral vision testing, and high-quality electroretinography according to a standardized protocol. As tools for in vivo high-resolution imaging of the retina such as confocal scanning laser ophthalmoscopy, optical coherence tomography (OCT), autofluorescence imaging, and fluorescein angiography become widely available, they should be included in clinical phenotyping. The complete physical examination should include blood pressure measurement and neurologic evaluation. Investigators should perform thoracic radiographs, abdominal ultrasound, and magnetic resonance imaging of the brain if indicated to rule out the presence of neoplasia. Objective assessments of olfaction such as electroencephalographic and behavioral olfactometry using eugenol and benzaldehyde may be helpful.

**Clinicopathologic and endocrinologic evaluation**
Results of a complete blood cell count, serum biochemistry analysis, and urinalysis should be recorded. Additional serum/plasma/whole blood samples should be stored at −80°C for future testing, including DNA analyses, testing for thyroid disease, and hyperadrenocorticism via serum concentrations of cortisol and adrenal sex hormones including 17-hydroxyprogesterone, progesterone, and estradiol before and after ACTH stimulation. To determine whether increased circulating cortisol is stress-related, catecholamine assessment should be considered. Continued testing of these hormones/markers following diagnosis would also be useful. Collaboration with internists to arrange measurement of many of these parameters...
in dogs with recent PU, PD, and PP of unknown cause may also provide useful premonitory information if any of these dogs subsequently develop SARDS.

**Immunologic assessment**

Circulating AAbs should be identified and characterized in dogs with SARDS and compared to an appropriate control population. These evaluations should include assessment of IgM and IgG titers, and their ratio. Following the discovery by Braus et al.\(^8\) of anti-NSE antibodies in SARDS-affected dogs, major efforts should be directed at identifying antibodies found exclusively in patients with SARDS and characterizing their target antigens and epitopes. Subsequent comparison of titers of AAbs in cases and controls will be critical, and canine cancers should be evaluated for expression of identified retinal antigens. Development of functional assays of AAbs to determine their binding affinity, cytotoxicity, and pathogenic potential would be valuable and may necessitate intraocular injection of these antibodies and/or vaccination with the target antigen in laboratory animals. An ultimate goal should be development of standardized arrays for larger scale AAb testing of affected and normal canine populations.

Considering that most autoimmune diseases are T-cell-mediated with secondary formation of autoantibodies,\(^1-13\) detailed investigation of the role of cellular immunity in SARDS is needed. Quantification of circulating CD4\(^+\) and CD8\(^+\) T, natural killer, and B cells by flow cytometry would determine whether SARDS dogs have abnormal profiles of these cellular subsets. Cells isolated from whole blood could also be functionally tested for responsiveness to retinal antigens in vitro. Major histocompatibility complex (MHC) profiles, which are skewed in several human autoimmune diseases, should be compared between affected and control dogs to further support an immune-mediated pathogenesis. Comparing cytokine concentrations in blood, aqueous humor, and vitreous between patients with SARDS and normal controls may also provide information about the immunologic mechanisms involved in photoreceptor death. Any immunologic assessments should distinguish between causative autoimmune mechanisms and immune responses that represent a normal consequence of retinal destruction.

**Genetic studies**

Although SARDS is not recognized as an inherited disease, a genetic predisposition is suggested by high disease prevalence in breeds such as dachshunds and miniature schnauzers. Detailed pedigree analyses and genomewide association studies (GWAS) will provide important data regarding potential genetic factors and may ultimately permit development of genetic markers for SARDS, thereby elucidating etiologic and pathogenic mechanisms, as well as permitting earlier diagnosis. Again, the careful selection and examination of control animals is critical for the success of such a study. Likewise, gene expression studies by microarray or RNAseq analysis of retinal and circulating lymphocytes should be expanded.\(^5,14\) This will be greatly facilitated by a donor system, which should be developed, maybe through specific breed clubs. Although, it remains possible that eyes donated some time after the onset of SARDS may no longer yield samples appropriate for immunologic or biochemical testing, genetic analysis should remain useful.

**Pathologic and histopathologic studies**

Although detailed histologic and molecular analyses of multiple organ systems may permit better understanding of the ophthalmic and systemic characteristics of SARDS, Think Tank members remain concerned that even the establishment of a body and tissue donation system will not produce sufficient useful samples in the acute or premonitory phase of disease and that analysis of archival tissue samples remains the most viable option for histologic or immunohistochemical studies. Very careful histologic examination of the central nervous system, including hypothalamus and pituitary gland, as well as adrenal and olfactory tissues is warranted to determine whether cells other than the retinal photoreceptors are being destroyed.

**Therapeutic trials**

It is generally believed that vision loss with SARDS is permanent and that there is no treatment that can prevent or reverse SARDS-related blindness,\(^5,14,19,20\) although anecdotal reports suggest that this may not be the case.\(^21,27,37,38\) The goal of the VAF initiative is to rigorously investigate potential therapies. If affected animals can be diagnosed before photoreceptors are permanently lost and the disease process reversed, it may be possible to successfully manage dogs with SARDS. Although an etiology and pathogenesis for SARDS must be unequivocally determined, potential treatments will likely continue to be tested. In order for these trials and their results to gain wider acceptance, patient selection criteria, treatment protocols, and outcome measures must be rigorous and consistently applied, proper controls are essential, and data must be submitted for peer review. Because no treatment is available for this disease, a double-masked, randomized, placebo-controlled study design would likely be considered ethically responsible provided that frequent interim data review is conducted during the study, and rescue criteria are identified a priori. Undoubtedly, such a study design would present the most convincing strategy to prove effectiveness of a new treatment. The most important treatment outcomes are objectively assessed restoration of visual performance in association with improved ERG and PLR parameters. Although pet owners’ satisfaction is critical, their assessment of visual performance at home is insufficient to document successful treatment, especially because dogs adjust to blindness through increased dependence upon nonvisual senses.

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Therapeutic trials could involve already clinically approved treatment strategies or new classes of drugs. Specifically, Think Tank members discussed the feasibility of producing a canine-specific IVIg, which may be more efficacious and better tolerated than the human product. Clinically approved drugs/antibodies against B cells, such as the anti-CD20 drug rituximab (Rituxan®; Genentech, Inc., South San Francisco, CA, USA) were also considered; however, many human-specific compounds may not target canine B-cell receptors and versions would have to be specifically developed for the dog.132

Treatment of endocrine abnormalities was also discussed. For example, use of a lignan phytoestrogen and melatonin combination has been advocated for treatment of dogs with atypical hyperadrenocorticism, where cortisol concentration is within reference limits, but levels of adrenal sex hormone concentrations are increased and mimic clinical signs of excess cortisol secretion.42 These compounds may decrease steroid hormone secretion by the adrenal gland and could potentially be beneficial for treating patients with SARDS, depending on how abnormal sex hormones and loss of photoreceptor function are linked.42

SUMMARIZING COMMENTS BY THINK TANK PARTICIPANTS

The following represent individual Think Tank members’ summary comments on the most critical and central elements in the ACVO-VAF’s goal to better elucidate predisposing factors, etiology, pathogenesis, clinical syndrome, and treatment options for SARDS in dogs.

(1) András M. Komáromy: ‘Regardless of the research methods used to investigate the pathogenesis of SARDS, the careful selection and examination of control animals is critical’.

(2) Kenneth L. Abrams: ‘Based on clinical and pathological findings in SARDS patients over years of original and review publications, there seems to be a neuroendocrine systemic trigger to the disease’.

(3) John R. Heckenlively: ‘There are striking similarities between SARDS and features seen in AIR. AIR in humans can present as a paraneoplastic event so it would help to document in SARDS if neoplasms are present, and if other systemic diseases co-exist. Mitochondrial mutations also can present with abrupt onsets, and mutational analysis of mitochondrial DNA from affected canines would be informative even if negative’.

(4) Steven K. Lundy: ‘As part of a research team that is studying the immune pathogenesis of human AIR, I am struck by the similarities in clinical findings between SARDS and AIR. It is too early to know whether these two syndromes are closely related in either immune or neuroendocrine features. Similarities or differences found between SARDS and AIR could significantly enhance our understanding of both diseases. Regardless of the cause of pathology, advances in screening and early interventions will likely be critical to preserving sight in either species’.

(5) David J. Maggs: ‘At the core of all future investigations of SARDS in dogs must lie a rational, orderly, committed, and rigorously standardized characterization of the clinical and epidemiological features of the disease or diseases that we currently group under this syndromic diagnosis’.

(6) Caroline M. Leeth: ‘Determining the pathogenesis of SARDS will require a concerted effort to study appropriate research participants with adequate controls in a systematic manner as this syndrome appears multi-faceted with the possibility for several etiologies’.

(7) Puliyur S. MohanKumar: ‘There is a distinct possibility of neuroendocrine involvement in SARDS which has not been explored thoroughly. Understanding the possible role of neurotransmitters in precipitating some of the co-morbidities observed in SARDS might provide important insights’.

(8) Simon M. Petersen-Jones: ‘Detailed early assessment of affected dogs is essential, and we should consider the possibility that more than one underlying etiology may be responsible for the SARDS presentation’.

(9) David V. Serreze: ‘As someone outside the veterinary community, I came away from the Think Tank with a view that SARDS is a syndromic range of diseases, and that better subtype stratification based on neuroendocrine, and immunological profiles is required to select optimized treatment strategies’.

(10) Alexandra van der Woerdt: ‘It will require the combined efforts of clinicians to identify affected animals and appropriate control dogs, and research scientist to help improve our knowledge about the etiology, pathogenesis and treatment of SARDS in dogs’.

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