SARDS CASE REPORT #3

Short-term hormone replacement in a Springer Spaniel affected with Sudden Acquired Retinal Degeneration Syndrome (SARDS)

Caroline D. Levin RN
18709 S. Grasle Road
Oregon City, OR 97045
Phone & fax: (503) 631-3491

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ABSTRACT

Objective: To describe the laboratory findings, hormone replacement therapy, and outcome of one dog affected with SARDS. Animal studied: A 13-year-old neutered male Springer Spaniel diagnosed with SARDS on May 30, 2005. The client reported persistent signs of PU, PP, confusion, and lethargy.

Procedure: An endocrinology and immunology assay was performed five months post-SARDS diagnosis, which indicated below normal levels of cortisol, IgA, IgG, IgM; and elevated levels of total estrogen. T3 and T4 were low normal. Hormone replacement therapy was initiated by the general-practice veterinarian. The dog received injectable Vetalog 0.3mg IM. Methylprednisolone/Medrol 4mg po, sid; and levothyroxine 0.5mg po, bid were dispensed. Bloodwork was repeated at one and five months after hormone replacement therapy was initiated. Hormone replacement therapy was discontinued after six months.

Results: Levels of cortisol, IgG, IgM returned to within normal limits by the fifth month. IgA levels also rose but were below normal. Total estrogen levels demonstrated a steady decline, although still elevated by the fifth month. T3 and T4 rose to the mid-normal range. The client reported improvement in clinical signs of PP, fatigue and confusion, but not PU. During the six-month period subsequent to hormone replacement therapy termination, the dog experienced increasing health problems, decreasing quality of life, and was euthanized.

Conclusion: Treatment with low, physiological-levels of replacement glucocorticoid and thyroid hormones improved some clinical signs and caused a decline in total estrogen production in this SARDS-affected dog. Withdrawal of treatment resulted in new health problems documented elsewhere in the literature as effects of elevated estrogen.

KEY WORDS: sudden acquired retinal degeneration syndrome, canine blindness, hypercortisolism, glucocorticoids, adrenal estrogen

Plain English Translation

Only the more complex terms and concepts have been translated, so please read the column on the left first.

PU = polyuria / excessive urination
PP = polyphagia/excessive appetite

This paper discusses the symptoms, treatment, and results of a Springer Spaniel diagnosed with SARDS. This dog had a blood test to measure thyroid hormones, adrenal hormones, and immunoglobulins (immune system function). The test indicated below normal levels of cortisol and immunoglobulins; and above normal levels of adrenal estrogen. The dog was then treated with a small steroid injection, a low dose of Medrol (a cortisol replacement), and thyroid hormone. The blood test was repeated twice more over the next five months. Cortisol levels and two immunoglobulin levels returned to normal. Elevated estrogen declined steadily. The owner noted some improvement in lethargy and excessive appetite. When treatment was discontinued the dog developed new health problems associated with rising estrogen.

DESCRIPTION OF THE CASE

The owner of a 13-year-old neutered male Springer Spaniel contacted the author for assistance in helping the dog adjust to blindness. The dog was diagnosed with SARDS by a certified veterinary ophthalmologist five months earlier on May 30, 2005. The client reported clinical signs of PU, PP, confusion, and lethargy, which developed prior to vision loss and persisted until present. The client reported that the dog was incontinent every four hours and constantly bumping into furniture.

Five months after vision loss (November 15, 2005) an endocrinology and immunology blood panel (National Veterinary Diagnostic Services, California) was ordered by the general practice veterinarian. Results indicated below normal levels of cortisol, IgA, IgG, IgM; and elevated levels of total estrogen. T3 and T4 were within normal limits at the low end of normal range. (table 1)

Table1. Immunology and endocrinology panel #1

Hormone		11-15-05 Results	Normal range
Cortisol	ug/dL	0.48 **L**	1.00-2.50
Total estrogen	pg/mL	25.32 **H**	20.00-25.00 (males)
T3	ng/dL	108.48	100.00-200.00
T4	ug/dL	2.16	2.00-4.50
IgA	mg/dL	43 **L**	70-170
IgG	mg/dL	781 **L**	1,000-2,000
IgM	mg/dL	80 **L**	100-200

Glucocorticoid replacement therapy was initiated by the dog's general-practice veterinarian. The dog received injectable Vetalog 6.25mg IM. In addition, methylprednisolone/Medrol 4mg po, sid and levothyroxine 5mg po, bid were dispensed to the client. (Manufacturers unknown.) The client also began preparing home-cooked meals for the dog.

On January 3, 2006 (one month after glucocorticoid replacement was initiated) the client reported less fatigue and better muscle tone in the dog. She also reported that the dog "is still very hungry but quiets more quickly after eating" and that although he "still bumps into everything, he does seem to find me in the room and lay next to me." The endocrinology and immunology panel was repeated. Results indicated a rise in cortisol, T3, T4, IgA, IgG, and IgM levels; and a decline in total estrogen. (table 2)

The dog was given several forms of *low-dose* cortisol replacements — one by injection, one in pill form. (The injection enters the body and goes to work quickly.) The dog was also given thyroid replacement hormone.

Over time, adrenal estrogen steadily declined and thyroid, cortisol and immunoglobulin (IgA, IgG, IgM) levels rose steadily, until most had returned to normal.

Table 2. Immunology and endocrinology panel #2

Hormone		1-03-06 Results	Normal range
Cortisol	ug/dL	0.56 **L**	1.00-2.50
Total estrogen	pg/mL	25.21 **H**	20.00-25.00 (males)
T3	ng/dL	113.16	100.00-200.00
T4	ug/dL	2.40	2.00-4.50
IgA	mg/dL	49 **L**	70-170
IgG	mg/dL	912 **L**	1,000-2,000
IgM	mg/dL	89 **L**	100-200

On March 27, 2006 (four months after glucocorticoid replacement was initiated) the client expressed interest in having a lipoma removed from the dog's back but reported that, "the vet won't remove it until the dog is off the medrol."

Lipoma = a benign fatty tumor

On April 24, 2006 (five months after glucocorticoid replacement was initiated) the endocrinology and immunology panel was repeated. Results indicated a further rise in cortisol, T3, T4, IgA, IgG, and IgM levels (cortisol, IgG, and IgM were within normal limits); and a further decline in total estrogen. (table 3)

Doctors typcially prescribe steroids such as prednisone and medrol in *large doses* when trying to *suppress the immune system*. This is referred to as an immunosuppressive or anti-inflammatory dose. It's typically used for cases of lupus, asthma, etc.

Table 3. Immunology and endocrinology panel #3

Hormone		4-24-06 Results	Normal range
Cortisol	ug/dL	1.29	1.00-2.50
Total estrogen	pg/mL	25.11 **H**	20.00-25.00 (males)
T3	ng/dL	121.71	100.00-200.00
T4	ug/dL	2.92	2.00-4.50
IgA	mg/dL	63 **L**	70-170
IgG	mg/dL	1,106	1,000-2,000
IgM	mg/dL	114	100-200

Consecutive results are compared in Table 4, Figure 1, and Figure 2.

The dog in this case report was prescribed a very *small dose* known as a physiological dose. This is the amount the body would normally make if it were healthy. It is unnecessary to take a dog off hormone replacement for such events as surgery. In fact, just the opposite is true. Patients need correct hormone levels (in this case, through hormone replacement therapy) in order to handle situations that are physically stressful.

Table 4. Comparison of consecutive blood panel results

		11-15-05	1-03-06	4-24-06
Cortisol	ug/dL	0.48 **L**	0.56 **L**	1.29
Total estrogen	pg/mL	25.32 **H**	25.21 **H**	25.11 **H**
T3	ng/dL	108.49	113.16	121.71
T4	ug/dL	2.16	2.40	2.92
IgA	mg/dL	43 **L**	49 **L**	63 **L**
IgG	mg/dL	781 **L**	912 **L**	1,106
IgM	mg/dL	80 **L**	89 **L**	114

Figure 1.

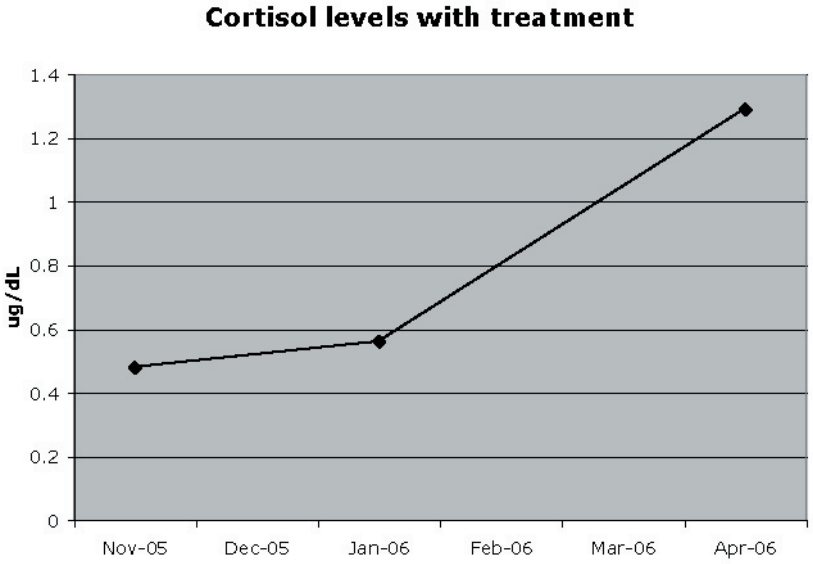
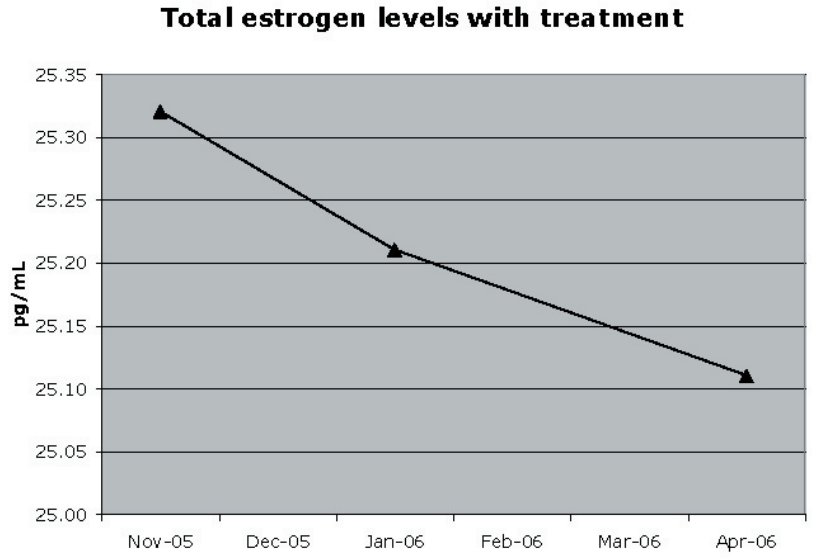


Figure 2.



Follow-up contact was lost for 10 months. When contact was re-established the client reported the following series of events. In June of 2006 (seven months after hormone replacement was initiated and one year after vision loss) hormone replacement therapy was discontinued by the client and general practice veterinarian. The client reported that, "we just felt it wasn't helping enough."

In September of 2006 (three months after hormone replacement therapy was discontinued) the dog developed fecal incontinence/ diarrhea in addition to PU every four hours. In December of 2006 (six months after hormone replacement therapy was discontinued) the dog developed rhinorrhea, which was unresponsive to antibiotic therapy (Amoxicillin and Baytril). This was followed by increased fatigue, anemia, renal failure, anorexia, and ataxia. The dog was euthanized on December 22, 2006, eighteen months post-SARD diagnosis, and six months after hormone replacement therapy was discontinued.

Perceptions differ between individuals. And although this dog demonstrated improvement in both bloodwork and some symptoms, progress was not swift enough for the owner. It's important to remember that adrenal exhaustion (see below) develops over many years and it can not be reversed immediately. Some dogs improve quickly, others recover more gradually.

rhinorrhea = runny nose
anorexia = loss of appetite
ataxia = stumbling or difficulty standing

DISCUSSION

Sudden Acquired Retinal Degeneration Syndrome is a rare but devastating condition characterized by acute-onset, irreversible, bilateral blindness in middle-aged dogs. Complete vision loss typically occurs between 24 hours and four weeks. Researchers describe a rapid loss of photoreceptor cell outer segments, followed by a more gradual degeneration of the remaining retina (1,2,3). Excitotoxicity (4) and apoptosis (5) are reported as two possible causes of photoreceptor cell death in SARDS.

Adrenal Gland Activity in SARDS

Dogs affected with SARDS routinely present with signs suggestive of Cushing's disease, or more specifically, signs of hypercortisolism close to the time of vision loss. (1,2,3,6,7) Early on, researchers speculated that hypercortisolism associated with SARDS was the physiological response to some unidentified stress (7). Only a minority of these dogs are actually diagnosed with Cushing's disease, however. (2,8) Dogs affected with SARDS also demonstrate elevated levels of adrenal sex hormones (androstendione, estradiol, progesterone, 17-OH progesterone, and testosterone) within the first year of blindness. (9,10) One explanation for this pattern of events is Selye's model of stress adaptation, which describes the progression from adrenal gland hyperactivity (hypercortisolism) to adrenal gland exhaustion (cortisol insufficiency). In Selye's model, adrenal activity is marked by three stages: alarm, resistance, and exhaustion. (11)

Many dogs with SARDS also have symptoms of excess cortisol (hunger, thirst, elevated liver enzymes, weight gain, confusion,depression,insomnia, panting, infections, etc.) but few are actually diagnosed with Cushing's disease. In addition, dogs with SARDS develop excess levels of adrenal sex hormones sometime within the first year of blindness. One explanation for this pattern is the stress model developed by Hans Selye MD, the father of endocrinology. In this model, he describes the transition from a period of excessive cortisol production to a period of low cortisol production called adrenal exhaustion.

Alarm Phase of Stress Adaptation (the normal response to stressors)

During the alarm phase the body responds to both physical and psychological stressors with increased adrenocortical activity. Hypothalamic-pituitary-adrenal (HPA) activity and the resulting cortisol secretion normally return to baseline levels when the stressor is resolved.

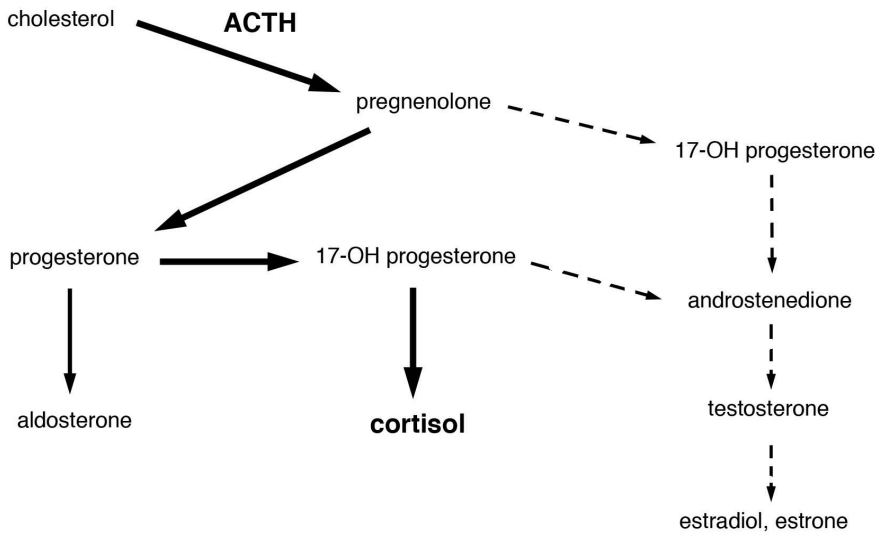
Resistance Phase of Stress Adaptation

The resistance phase occurs following a prolonged period of stress. Elevated cortisol production continues but falls to a level *only slightly above* normal. Prolonged exposure to elevated cortisol results in loss of hypothalamic sensitivity. Cortisol production continues unabated. (12) Researchers involved in the neuroendocrine theory of aging have also described it as adrenal maladaptation or hyperadaptosis and consider it to be a precursor of Cushing's disease. (13,14) This may explain why some SARDS-affected dogs eventually test positive for Cushing's disease.

During the resistance phase, adrenal activity adapts to chronic stressors by initiating a preferential pathway of steroidgenesis. Levels of precursors (pregnenolone, progesterone, and 17-OH progesterone) decline as they are consumed by continuous cortisol production. Sex hormone production is also sacrificed in preference for cortisol production. This scenario is referred to as the "pregnenolone steal." (15,16) (figure 3)

Figure 3

Steroid Biosynthesis During Resistance Phase



When a stressor starts, the brain (the **h**ypothalamus) signals the **p**ituitary gland to release ACTH. This hormone signals the **a**drenal glands to increase cortisol production. (This connection of glands/organs is called the HPA axis.) When the stressor stops, so does this chain of events. (The brain recognizes that there is sufficient cortisol in the bloodstream. This signals the pituitary gland to reduce ACTH production, and as a result, cortisol production returns to normal.)

However, if the stressor is non-stop, cortisol is constantly secreted. The brain becomes numb to it and never signals the adrenal gland to relax. The adrenal gland becomes stuck in overdrive.

The adrenal gland adapts to chronic stress by rerouting normal hormone production to meet the high demand for cortisol. This is an important point: *the production and flow of adrenal hormones is flexible and adaptable*.

How to read these charts:

Large, bold text indicates hormones that are being produced in excess.

Bold arrows indicate the pathway where the most activity is occurring.

Small or broken arrows indicate reduced hormone production.

Exhaustion Phase of Stress Adaptation

In the final phase of the general adaptation syndrome—exhaustion—the adrenal glands can no longer sustain elevated cortisol production. Both humans and dogs passing into this stage typically present with declining levels of serum cortisol and thyroid hormones (T3 and T4) and rising levels of total estrogen. (17,18)

Hyperestrogenism produces effects similar to hypercortisolism including: fatigue, depression, irritability, seizures, and hyperpigmentation, in humans. (19,20,21,22) Pancreatitis, elevations in blood glucose, alkaline phosphatase, serum amylase, cholesterol, and triglycerides are also reported. (23,24,25) Elevated estrogen causes aggression, renal disease, and bone marrow depression in dogs (26,27,28); and hepatic dysfunction, histamine release, thyroid binding and immunoglobulin suppression in both species. (21,24,26,28,29) Estrogen-treated rats experience PU/PD and an inability to concentrate urine. (30,31)

Increased production of adrenal estrogen depends on hormone precursors such as progestagens (progesterone, 17-OH Progesterone) and androgens (androstendione, testosterone), which may also be elevated. Elevated progestagen levels impair glucose tolerance, increase body core temperature, and stimulate appetite and weight gain in humans (32,33). Elevated androgen levels result in acne, central obesity, alterations in hair growth patterns. (34)

Glucocorticoid replacement is reported to normalize excess adrenal estrogen production in both dogs and humans. (17,18)

The dog discussed here demonstrated several of these patterns. Similar to other SARDS-affected dogs, this dog experienced elevated adrenal sex hormone levels within the first year of blindness. Prior to treatment this dog demonstrated below normal levels of cortisol and in conjunction with elevated estrogen as described in Selye's model of adrenal exhaustion. This dog experienced suppressed immunoglobulin levels (table 1) which are also indicative of hyperestrogenism and adrenal exhaustion.

When the adrenal glands can no longer produce cortisol, they produce another, somewhat similar hormone instead—adrenal estrogen. *The symptoms of adrenal estrogen closely resemble the symptoms of excess cortisol.*

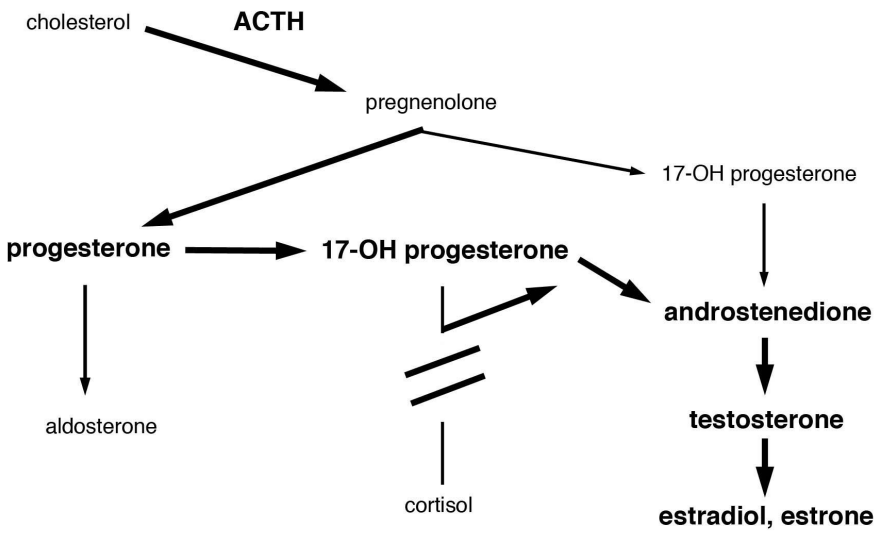
Hyperpigmentation = darkening of the skin
alkaline phosphatase = a liver enzyme
Renal disease = kidney disease
Bone marrow depression = immune system failure/ cancer
Hepatic dysfunction = liver disease, elevated liver enzymes
Histamine release = runny nose, red, itchy eyes, increased allergies
Thyroid binding = thyroid hormone molecules are "bound up" and cannot function
immunoglobulin suppression = low levels of IgA, IgG, IgM

The spaniel in this report followed these patterns. The dog experienced low cortisol levels in conjunction with high estrogen levels. This illustrates that this dog had moved into the adrenal exhaustion phase by five months after blindness.

As cortisol production waned, adrenal activity "spilled over" into the adjacent pathway causing a rise in sex hormone production. (figure 4) These results suggest that adrenal exhaustion (cortisol depletion) had developed within five months of vision loss.

Figure 4.

Steroid Biosynthesis During Adreno-cortical Exhaustion Phase



Additionally, as reported in other dogs and humans, this dog's elevated estrogen levels declined following oral replacement of glucocorticoid and thyroid hormones. Reestablishment of normal glucocorticoid levels is suspected to interrupt chronic ACTH stimulation (17,18) and curtail the "spill-over" effect.

When the adrenal glands could no longer produce cortisol (they were exhausted) the adrenal gland activity "spilled over" to the adjacent hormone pathway. This resulted in elevated levels of adrenal estrogen. *When one path is blocked, hormone activity was rerouted down another pathway.* A good analogy would be boating down a river. If a dam was built across the river, the water would back up and you would have to steer your boat down a different branch of the river to continue on your trip.

When cortisol levels were brought back up to normal with medication (Medrol and the injection) the brain realized this and stopped stimulating the adrenal glands. The adrenal glands relaxed. This reduced the "spill over" and adrenal estrogen levels returned to normal.

Apoptosis / Programmed Cell Death

Cellular mitochondria play a key role in apoptosis. Factors such as viral infections, pro-oxidants, neurotoxins, ishchemia, and hormone levels trigger apoptosis and damage inner and outer mitochondrial membranes. This is known as the premitochondrial phase of apoptosis. Membrane damage induces cellular changes such as increased calcium levels and antioxidant depletion, resulting in loss of mitochondrial membrane function. This is referred to as the mitochondrial phase. During the final phase of apoptosis (the postmitochondrial phase) caspases and other apoptosis-inducing factors are released, degrading cellular components. (35)

The process of apoptosis (retinal cell destruction) includes many steps, but very simply put, tiny organs inside each cell (the mitochondria) are destroyed. Once these are destroyed, enzymes break down the the rest of the cell.

The plasma membrane of photoreceptor cells contains gated ion channels, which control the influx of calcium ions (Ca2+) into the cells. In photoreceptor outer segments Ca2+ controls light adaptation. In photoreceptor inner segments Ca2+ regulates cell metabolism, glutamate release, gene expression, and cell death. (36) In pathological conditions of cellular overload, especially in conjunction with oxidative stress, mitochondrial Ca2+ uptake triggers collapse of mitochondrial membrane potential and delayed cell death. (37)

Calcium passes through retinal cells and helps produce vision. When too much calcium enters the retinal cells it can destroy the mitochondria and initiate apoptosis or cell death.

Apoptosis is a common final pathway in multiple retinal disorders including glaucoma. It is also prevalent in other systems such as the central nervous system (CNS) and immune system. Apoptosis is modulated in these systems is by glucocorticoids and sex hormones. Glucocorticoid excess is reported to cause apoptosis in thymus and T-cells of mice, cells of the brain and CNS. (38,39) Glucocorticoid excess induces intracellular calcium overload and excitotoxicity. (40) The retina has many steroid receptors resulting in steroid accumulation in the retina. (41)

Both cortisol and estrogen are capable of letting excess calcium into cells.

Adrenal sex hormones (estrogen and progesterone) oppose glucocorticoid-induced apoptosis by providing neuroprotection in some systems. Systemic administration of estradiol has been shown to protect rat retinas from photoreceptor degeneration. (42) Estrogen rapidly modulates intracellular signaling pathways by activating protein kinase C in certain cell types. This enzyme plays a key role in regulating apoptosis. (43) Sudden withdrawal of estrogen levels (estrogen deficiency) leads to increased apoptosis in brain tissue of chicks. (44) Alternately, accumulation of *excessive* estrogen may also contribute to apoptosis. (41)

When estrogen and progesterone are at normal levels they protect some cells (mostly nerve and brain cells) from self-destruction. However, when these hormone levels are abnormal, it may set the stage for apoptosis.

The role of progesterone as an anti-apoptotic agent is less clear. This may be influenced by which specific genes are responsible for apoptosis in specific systems. (45) Sudden withdrawal of progesterone increases excitoxicity and apoptosis in brain tissue of mice (46) but had no anti-apoptotic effect in rat neural retinal tissue. (47)

An Endocrine Model of SARDS

To date, SARDS has generally been addressed as a retinal pathology, however increasing evidence suggests that sudden retinal degeneration is merely one clinical sign of broader adrenal gland dysfunction. The author proposes the following model to describe the clinical course of SARDS-affected dogs and potential, therapeutic interventions.

Stage I of SARDS: Hormone-induced apoptosis / vision loss

At the onset of blindness, SARDS-affected dogs clinically demonstrate the resistance phase of the stress adaptation response. Cortisol levels are only *slightly* elevated during the resistance phase, (11) which is sufficient to cause signs of hypercortisolism but typically insufficient for a positive Cushing's diagnoses.

During the resistance phase estrogen and progesterone production is suppressed in favor of cortisol production (15,16) (figure 3). Elevated adrenal steroid hormones increase intracellular Ca2+, which upregulates genetic expression and cell death in photoreceptor cell inner segments. (36) The author submits that this period of elevated steroid production triggers excitotoxicity and initiates apoptosis in SARDS.

When dogs first go blind from SARDS they appear to be in the resistance phase of the stress response: producing too much cortisol. This hormone imbalance may trigger retinal cell death.

Stage II of SARDS: Advanced adrenal disease

SARDS-affected dogs can develop at least two distinct adrenal-related pathologies: Cushing's disease and adrenal exhaustion. These conditions arise from the prolonged period of elevated cortisol production during the resistance phase of stress adaptation.

In time, some SARD dogs will develop Cushing's disease and another portion will develop adrenal exhaustion.

Approximately 20% of SARDS-affected dogs will ultimately develop Cushing's disease. Researchers attribute the chronic activation of the HPA axis in hyperadaptosis, the precursor phase of Cushing's disease. (13)

The longer an individual produces excess cortisol, the greater the chances of developing Cushing's disease. Dogs diagnosed with "borderline" Cushing's may be at a greater risk of developing SARDS.

Another portion of SARDS-affected dogs will develop adrenal exhaustion as demonstrated by rising adrenal sex hormone activity and declining cortisol production. (9,48) Elevations in sex hormones result in the long-term complaints from the owners of these dogs.

In the months that follow blindness hormone levels may reverse. Cortisol drops too low and estrogen and the other sex hormones rise too high. The sex hormones (especially estrogen) can mimic many of the same symptoms caused by excess cortisol.

When clinical signs of hyperestrogenism are present in conjunction with normal cortisol values, a diagnosis of atypical Cushing's disease is sometimes made. (49) The author suggests that the terms atypical Cushing's, hyperestrogenism, and adrenal exhaustion may all describe a similar state.

Atypical = *non*-typical. In this case, having the symptoms of Cushing's disease without a Cushing's tumor. Estrogen is actually causing the symptoms.

SARDS-affected dogs are frequently dismissed as "otherwise healthy." The author submits that this may not be an accurate assessment of these dogs if they are routinely developing adrenal exhaustion (cortisol insufficiency) and hyperestrogenism. Elevated adrenal sex hormone activity can cause poor quality of life issues, which in turn, may cause the client to needlessly euthanize the dog.

In the author's opinion dogs with SARDS are *not* otherwise healthy and their adrenal hormones should be periodically measured to prevent and protect these dogs from the damaging effects of excess estrogen. Three of the most damaging effects of excess estrogen are liver degeneration, kidney failure, and cancer growth.

The Springer Spaniel described here developed clinical signs (anemia, rhinorrhea, renal failure, anorexia and ataxia) consistent with advanced adrenal fatigue, once hormone replacement therapy was terminated. *Hyperestrogenism* is reported to cause lethargy and non-regenerative anemia in dogs, (50,51) hypertension, increased mast-cell activity, and histamine release in humans; as well as, renal disease in both species. (19,20,27) *Hypocortisolism* is reported to cause anorexia, diarrhea, weakness, and lethargy in dogs, as well as vomiting and hypoglycemia. (51)

Once hormone therapy was discontinued, the dog relapsed into adrenal fatigue (low cortisol, high estrogen). The dog's symptoms progressed to a point requiring euthanasia.

anemia = low red blood cell count
rhinorrhea = runny nose
renal failure = kidney failure
anorexia = loss of appetite
ataxia = difficulty standing
mast cells = secrete histamine which causes the nose to run, eyes to tear
Hypertension = high blood pressure resulting in kidney damage
Bone marrow depression = failure of the immune system/cancer growth
Histamine release = runny nose, red, itchy eyes

RECOMMENDATIONS

The dogs described in this paper and the author's previous paper (48) both benefited from low-level glucocorticoid and thyroid hormone replacement therapy during the adrenal exhaustion phase. Hormone replacement during adrenal exhaustion had no reported effect on the vision of this SARDS-affected dog. However, the beneficial effects were evident in laboratory values and some clinical signs. Clients with SARDS-affected dogs should be encouraged to pursue estrogen/adrenal sex hormone testing and glucocorticoid/thyroid hormone replacement therapy for adrenal exhaustion, if indicated.

It is unknown at this time whether exhausted adrenal gland function can be fully repaired with hormone replacement therapy. Therefore, hormone replacement therapy should be considered as a *long-term* therapy for these dogs.

Future research should include consecutive measurements of adrenal sex hormone activity, including testing *at the onset* of blindness and continuing for a period of up to a year or more. Such data would provide a more comprehensive picture of adrenal activity in SARDS-affected dogs. Slightly elevated cortisol production, in conjunction with suppressed adrenal sex hormone activity at the time of vision loss (as compared to later readings) would suggest the resistance phase of the stress adaptation response. Such a scenario would further implicate chronic stress for its involvement in SARDS.

If dogs with SARDS were to have their adrenal hormones tested at the time of blindness, and the pattern was indicative of the resistance phase, it would further support the argument that SARDS occurs during a prolonged period of stress. The author's previous research on this topic suggests that this stress may be physical in nature (physical irritation) stemming from the modern-day diet, pesticide exposure, and over vaccination.

This paper supports previous studies, which have implicated excitotoxicity, (4) apoptosis, (5) the stress response (7,52) and adrenal dysfunction (9,48) for their involvement in SARDS.

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