SARDS case report #7

# Reversal of blindness and elevated adrenal activity in a Springer Spaniel with Sudden Acquired Retinal Degeneration

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ABSTRACT

**Purpose.** To describe the clinical and laboratory findings, treatment, and outcome of one dog affected with Sudden Acquired Retinal Degeneration (SARD). **Methods.** Animal studied: an eleven-year-old, male Springer Spaniel with PU/PD, lethargy, confusion, seizures, and head tics six weeks prior to SARD-onset. An ACTH test was negative for Cushing's disease. An endocrine-immune (E&I) panel indicated elevated total estrogen, low cortisol, and low immunoglobulins. The general practice veterinarian administered dexamethasone sulfate 2.2mg IM and triamcinolone acetonide 0.5mg IM; followed by medrol 3mg PO SID, Soloxine 0.5mg BID, and Sulfasalazine 500mg PO BID. The owner prepared a home-cooked diet and dispensed magnesium taurinate one-half tablet SID, phosphatidylserine 200mg SID, and Cell Advance 880 one tablet BID. The E&I panel was repeated after six weeks. The owner declined a repeat electroretinogram. **Results**. E&I panel indicated improvement in all parameters. Total estrogen, IgG, and IgM were within normal limits. T3 and T4 levels rose toward mid-normal range. The owner reported complete resolution of PU/PD. lethargy, confusion, seizures, and head tics within three months of treatment. Shortly thereafter, the dog successfully negotiated an obstacle course administered by the general practice veterinarian. The owner described additional episodes of functional vision. **Conclusion**. Prompt treatment restored functional vision and alleviated signs of adrenal excess. Owners of SARD-affected dogs should be encouraged to pursue prompt estrogen/sex hormone testing for signs of elevated adrenal activity, and a comprehensive approach to adrenal and retinal complaints. The author discusses hormone replacement, dietary, and nutraceutical therapies.

Plain English translation

Six weeks before this dog was diagnosed with SARD he developed signs of excess adrenal gland activity, including excessive thirst and urination (PU/PD), lack of energy, confusion, seizures and head-tics (head-bobbing). The dog did not have Cushing's disease. Instead, his labwork showed low cortisol and *elevated estrogen*, which mimics many of the symptoms of cortisol.

The owner immediately switched the dog to a home-cooked diet. This was followed by hormone therapy to replace the low levels of cortisol. Finally, a variety of supplements were added to help protect the retina until hormone levels returned to normal. After three months, vision returned and adrenal symptoms resolved.

DESCRIPTION OF THE CASE

An 11-year-old neutered male Springer Spaniel presented with signs of elevated adrenal activity including PU/PD, lethargy, confusion, seizures, and head-tics. The owner described him as having been a "red itchy dog for years" with a history of skin, ear, and conjunctival infections. He was also described as having a "delicate stomach." The general practice veterinarian ordered a thyroid panel, which found T3 and T4 within normal limits, but Free T4 below normal. (table 1) An ACTH-stimulation test was negative for Cushing's disease. (table 2)

Table 1. Thyroid panel on Soloxine 0.5mg BID (Antech Diagnostics)

| **Thyroid panel** | **02-23-07** | **Normal range** |
|---|---|---|
| T3 | 62 | 45-150 ng/dL |
| T4 | 1.7 | 1.0-4.0 ug/dL |
| Free T4 by equilibrium dialysis | 3 | 8-40 pmol/L |

Table 2. ACTH stimulation test (Antech Diagnostics)

| **ACTH stimulation test** | **03-08-07** | **Normal range** |
|---|---|---|
| baseline cortisol | 9.0 | 1-5 ug/dL |
| post-ACTH cortisol | 16.8 | 5.5-20 ug/dL |

Six weeks later the dog experienced bilateral vision loss and was diagnosed with Sudden Acquired Retinal Degeneration (SARD) via electroretinogram (ERG).

The owner switched the dog to a home-cooked diet consisting of approximately 50% (by volume) ground fruits and vegetables such as carrots, apples, bananas, green beans, broccoli, winter and summer squash; and 50% (by volume) protein sources such as ground beef, chicken, turkey, pork, eggs, and sardines. Protein sources were

This dog had a long history of digestive upset and skin allergies, which further suggested he didn't have Cushing's disease (excess cortisol). Cortisol is the anti-inflammatory hormone and would have soothed irritation. Estrogen, however, is the ***pro-***inflammatory hormone. Inflammation is a common complaint when estrogen levels are high.

Low levels of "free T4" also suggest elevated estrogen as an underlying problem (estrogen binds with thyroid). Only a small percentage of thyroid hormone circulates "freely" in the body, that is, unbound by proteins. This is the portion the body can actually use. This dog had very little free T4 hormone available.

During adrenal exhaustion, some Cushing's tests give faulty results. For example, in the urine cortisol/creatinine test, precursor hormones are falsely read as cortisol. If the same is true for the ACTH test, high baseline cortisol readings may be a combination of cortisol plus deoxycortisol. (figure 1)

ultimately restricted to ground pork, pork liver, and sardines as others were poorly tolerated and resulted in loose stools and flatulence. The diet was supplemented with Tums extra-strength (GlaxoSmithKline) three tablets SID as a source of dietary calcium.

Two weeks post SARD-onset, the general practice veterinarian ordered an endocrine-immune (E&I) panel. Results indicated elevated levels of total estrogen, and low levels of cortisol and immunoglobulins. T3 and T4 were within the bottom 18% of normal range. (table 3)

Table 3. Endocrine-immune panel (National Veterinary Diagnostic Services)

| **Hormone** | **04-17-07** (Initial) | **06-12-07** (Follow-up) | **Normal range** |
|---|---|---|---|
| Cortisol | 0.91 | 0.99 | 1.00-2.50 ug/dL |
| Total estrogen | 25.04 | 24.92 | 20.00-25.00 pg/mL (males) |
| T3 | 105.49 | 109.34 | 100.00-200.00 ng/dL |
| T4 | 2.28 | 2.47 | 2.00-4.50 ug/dL |
| IgA | 61 | 68 | 70-170 mg/dL |
| IgG | 1025 | 1152 | 1,000-2,000 mg/dL |
| IgM | 99 | 113 | 100-200 mg/dL |

A comprehensive plan was initiated to address both adrenal and retinal complaints. The general practice veterinarian administered dexamethasone sulfate 2.2g IM (Antech) and triamcinolone acetonide 0.5 IM (Bristol-Myer Squibb). This was followed by medrol 3mg PO SID (Barr Laboratories) and Sulfasalazine 500mg PO BID (Qualitest Pharmaceuticals) given 30 minutes prior to oral hormone tablets for improved intestinal absorption. A pre-existing prescription for Soloxine 0.5mg BID (Daniels Pharmaceuticals) was maintained. One month subsequently, medrol was increased to 4mg PO SID.

In addition, the client dispensed magnesium taurinate (Nutraceutical Sciences Institute) one-half tablet SID, phosphatidylserine (Nutraceutical Sciences Institute) 200mg SID, and an antioxidant—Cell Advance 880 (VetriScience) one tablet BID. The E&I panel was repeated after six weeks. The owner declined a repeat electroretinogram.

Homemade diets should include a wide variety of ingredients. This dog had difficulty digesting a number of protein sources, so the owner limited them to those he tolerated best.

This dog had classic adrenal exhaustion: estrogen was high, cortisol and immunoglobulins were low. These immunoglobulins are the “soldiers” of the immune system. IgA lines the skin and mucous membranes. When IgA levels are low, irritants can pass deeper into the body-causing inflammation and infections (eye, bladder, skin and ear infections). Research tells us that the most common cause of high estrogen is low cortisol production.

This dog was given several very small cortisol replacement injections to calm the GI tract, after wihich, the body would be better able to absorb oral tablets. Several of these were supplements to protect the retina.

## RESULTS

Repeat E&I panel indicated improvement in all parameters. Total estrogen, IgG, and IgM were within normal limits. T3 and T4 levels rose toward mid-normal range. PU/PD resolved one week after hormone replacement was initiated. Lethargy, confusion, seizures, and head tics resolved after three months.

At this time, the owner began reporting anecdotal episodes that suggested the return of functional vision. In the first incident she picked up a bottle of imitation butter at the dinner table, which caused the dog to run and hide. She stated that in the past she had "disciplined him with a water squirt bottle, which he hated."

The dog successfully negotiated an obstacle course in the veterinary clinic exam room, moving to avoid obstacles. The general practice veterinarian confirmed a degree of functional vision.

Shortly thereafter, the dog was relocated to a summer residence. The owner described the dog successfully "maneuvering through trees and picnic tables" and that he was "able to see the porch steps, the edge of the porch, and edge of the dock."

Nine months after SARD onset the owner described the dog's vision as intact but slightly deteriorated, "He sees movement mostly and it is definitely linked to bright lighting conditions."

The owner declined to return to the veterinary ophthalmology clinic. She described the long trip as "extremely stressful to the dog" and she chose not to risk his current level of vision to any effects that stress might have upon him.

## DISCUSSION

Dogs affected with SARD routinely present with signs suggestive of hypercortisolism (1,2,3,4,5) but only a minority are diagnosed with Cushing's disease. (2,6) Early on, researchers speculated that this hypercortisolism was the physiological response to some unidentified stress (5). SARD-affected dogs also demonstrate elevated levels of adrenal sex hormones (androstenedione, estradiol, progesterones, and testosterone) within the first year of blindness. (7,8) 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. (9)

During the alarm phase the body responds to stressors with increased hypothalamic-pituitary-adrenal (HPA) activity and cortisol secretion. Cortisol production returns to normal when the stressor is resolved. This is the normal, healthy response to psychological and physical stressors (irritation).

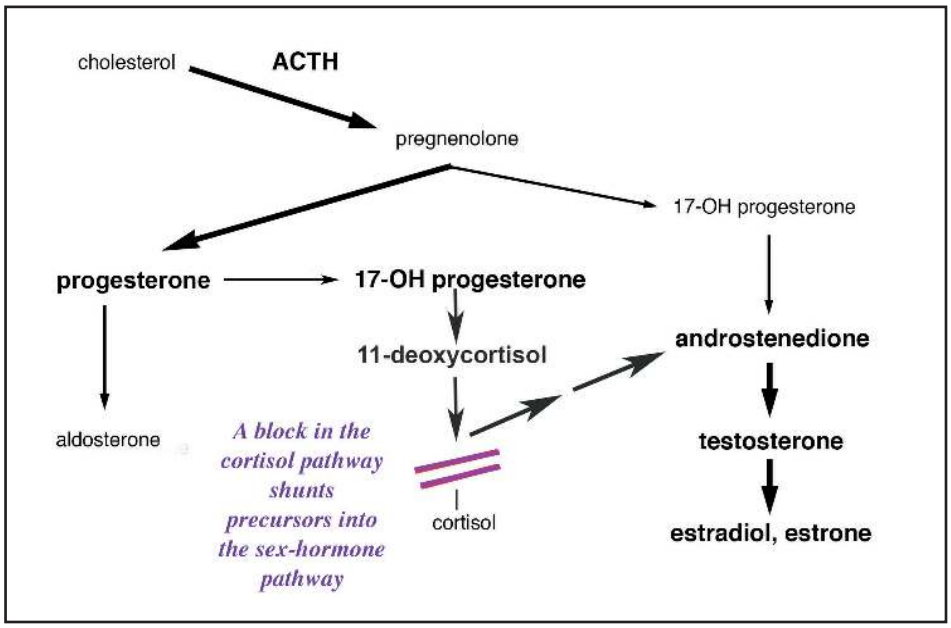
Hans Selye is known as the "father of endocrinology". Many people know his stress response as the fight or flight reaction.

In the first phase of Selye's stress response, the adrenal glands increase cortisol production when faced with a short-term stress or irritatant. When that stressor stops, hormone levels drop back to normal.

The resistance phase occurs following a prolonged period of stress. Elevated cortisol production continues but falls to a level only slightly above normal. The HPA feedback loop fails. Cortisol production continues unabated. (10)

In the final phase—exhaustion—the adrenal glands are unable to sustain elevated cortisol production. Clinical signs result from accumulating levels of precursors, such as 11-deoxycortisol, and sex-hormones, such as androstenedione, estradiol, and estrone. (figure 1) This pattern has been recently identified in SARD-affected dogs. (11,12)

Figure 1. Sex-hormone accumulation during adreno-cortical exhaustion




## Hormone activity during adrenal exhaustion

Hyperestrogenism produces effects similar to hypercortisolism including, fatigue, confusion, depression, agitation, pancreatitis, and seizures in humans, (13-20) renal disease, bone marrow depression, and anemia in dogs (20,21,23); immunoglobulin suppression, hepatic dysfunction, increased mast cell activity, and thyroid binding in both species. (12,16,24,25) Estrogen-treated rats experience PU/PD and an inability to concentrate urine. (26,27) Increases in related sex-hormones, such as progesterone, androstenedione, and testosterone cause increased heat intolerance, acne, obesity, and alterations in coat growth. (28, 29, 30)

However, if stress or irritation is unending the adrenal glands get stuck in "overdrive" pumping out more cortisol than is necessary.

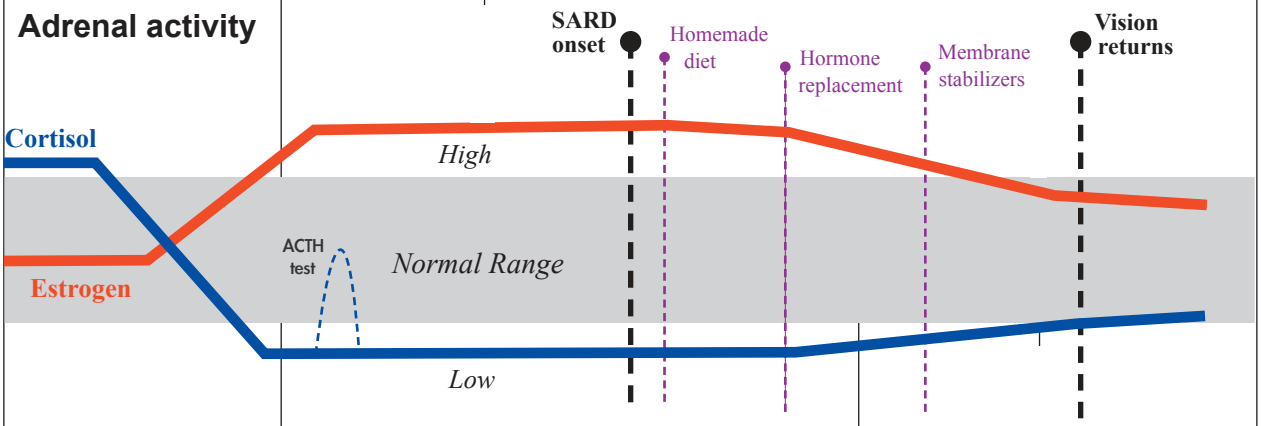
Over time the adrenal glands simply become exhausted from this effort. They can no longer convert the precursor hormones (the building blocks) into cortisol. These precursors pile up and spill over into the adjacent pathway—the sex hormone pathway. The end result is high levels of estrogen and other sex hormones.

Excess estrogen causes symptoms very similar to excess cortisol. This is why it's often mistaken for Cushing's disease. Some of these symptoms include high levels of: triglycerides, cholesterol, lipase, and liver enzymes; elevated BUN, creatinine or protenuria; increased histimine release (allergies, red eyes); low immunoglobulin levels (cancer and autoimmune disease); and incontinence.

As other sex hormones rise, they cause excessive panting, excessive hunger, weight gain, and changes in the how the coat grows.

Severely depleted cortisol, causes anorexia, abdominal pain, weight loss, vomiting, diarrhea, organ failure, and weakness. Without treatment, severe hypocortisolism is fatal. (31,32) Based on clinical presentation and laboratory findings, this dog experienced the adrenal exhaustion phase at the onset of SARD. (table 4)

Table 4. Overview of clinical presentation, diagnostics, and corresponding adrenal activity

| | February 2007 | March 2007 | April 2007 | May 2007 | June 2007 |
|---|---|---|---|---|---|
| **Clinical signs** | PU/PD<br>lethargy<br>confusion<br>seizures<br>head-tics | PU/PD<br>lethargy<br>confusion<br>seizures<br>head-tics | PU/PD<br>lethargy<br>confusion<br>seizures<br>head-tics | lethargy<br>confusion<br>seizures<br>head-tics | none |
| **Diagnostics** | ACTH: Normal | | | | |
| | | | estrogen: **H**<br>cortisol: **L**<br>IgA: **L**<br>IgG: N<br>IgM: **L** | | estrogen: N<br>cortisol: **L**<br>IgA: **L**<br>IgG: N<br>IgM: N |
| **Adrenal activity** |  | | | | |
| | **Adrenal exhaustion — initial —**<br><br>Following a prolonged period of stress or irritation, adrenal gland function becomes exhausted. Cortisol production begins to fail. Previously elevated levels of cortisol temporarily drop within the normal range. | | **Adrenal exhaustion — advanced —**<br><br>As adrenal exhaustion progresses, cortisol levels drop below normal. The brain attempts to increase cortisol production (via continual ACTH secretion). This only increases levels of precursors and sex-hormones (estrogen, progesterone, and androgens). Elevated sex-hormones cause clinical signs that mimic Cushing's disease.<br><br>During this phase, adrenal glands may still be able to "rise to the challenge" of an ACTH test, but they produce insufficient cortisol for daily needs. | | **Recovery**<br><br>The hypothalamus, perceives the presence of prescription glucocorticoids and reduces ACTH stimulation. Exhausted adrenal glands relax. Estrogen levels return to normal. Clinical signs improve. Prompt treatment of adrenal dysfunction may reduce photoreceptor calcium influx, thereby sparing some cells from destruction. |

**Retinal activity during adrenal exhaustion**

Apoptosis is a common final pathway in multiple retinal disorders including SARD. (33) It is also prevalent in other systems such as the central nervous system and immune system. Apoptosis is modulated in these systems is by steroid hormones such as cortisol and sex hormones. (34,35)

Retinal photoreceptor cell membranes contain gated ion channels, which control the influx of calcium ions (Ca++) into these cells. In photoreceptor outer segments, Ca++ controls light adaptation. In photoreceptor inner segments, Ca++ regulates cell metabolism, glutamate release, gene expression, and cell death. (36)

In pathological conditions of steroid hormone excess, Ca++ influx increases. Elevations in intracellular calcium, along with pro-oxidants, neurotoxins, and ishchemia damage the cell mitochondria. Caspases and other apoptosis-inducing factors are then released, degrading cellular components. (37) In SARD cases, retinal abnormalities typically do not develop until weeks or months after SARD onset, indicating that apoptosis is not immediate. (2,3)

**Therapies utilized in this case**

The goal of therapy was threefold: correct adrenal dysfunction, stabilize retinal cell membranes, and protect internal photoreceptor cell structures. The author speculated that if cellular structures were protected from damage while hormone levels normalized, some photoreceptor cells might be spared from destruction.

Commercial pet food may act as a chronic irritant in some dogs and a causal factor in adrenal exhaustion and the resulting sex-hormone excess. SARD-affected dogs fed homemade, grain-free meals, demonstrate fewer signs of elevated adrenal activity when compared to those eating commercial pet food. (38)

Low-dose glucocorticoid replacement therapy has been reported to reduce excess sex-hormone production in humans and SARD-affected dogs. (11,12,20,39-43) Normalizing levels of serum estrogen would be expected to normalize the rate of Ca++ influx, mitigating cellular damage.

Magnesium has long been reported to have membrane-stabilizing effects and to modulate cellular Ca++ influx. (44) When chelated with taurine, magnesium becomes highly absorbable (45) and provides a

In SARD cases, retinal cells are destroyed by a self-destruct message known as apoptosis. It starts like this:
When adrenal hormones are high they permit too much calcium into retinal cells. (A little calcium is necessary for vision but high levels damage the tiny internal organs of the cells.) Once these tiny organs are damaged, the self destruct message is put into action.

However, we also know that cell death is not immediate in SARD cases. There is a window of opportunity that spans from a few weeks to perhaps a few months. So *early treatment* is very important.

The treatment in this case had three goals:

1) Repair the adrenal problems (by reducing chronic irritants like processed pet-food) and restoring proper cortisol levels, which in turn, normalizes estrogen.

2) Reduce excess amounts of calcium that were likely flowing into the retinal cells (with the use of magnesium, taurine, etc.)

3) Protect the internal organs of the retinal cells until the hormone levels were back to normal.

source of taurine. This amino acid also acts as a membrane stabilizer, exhibits anti-apoptotic, and anti-oxidant activity in the rat retina. (46).

Adenosine, another amino acid, is reported to work in concert with magnesium and taurine. Adenosine inhibits glutamate-induced calcium influx and voltage-gated calcium currents in rat retinas. (47) Sardines and liver were provided once weekly as a dietary source of this amino acid.

The anti-oxidant properties of Vitamin A, C, and E in the human and rat retina are well described in the literature.

Phosphatidylserine (PS), an Omega-3 phospholipid, plays a key role in cellular metabolism and maintains membrane stability. In humans, stress and aging are associated with derangement of cell membrane lipid composition. Oral PS may improve clearance of intercellular waste products. (48)

It is worth clarifying the role of calcium in the therapies described here. Dietary calcium is a necessary nutrient for proper skeletal and dental health, and one not provided by a home-cooked diet, hence the addition of a calcium supplement. The aim of membrane-stabilizing therapies was to mitigate excessive levels of calcium from accumulating *within retinal photoreceptor cells*.

Normal levels of calcium in the bloodstream are not dangerous to retinal cells. It's only when more calcium than normal *is allowed to enter the cells of the retina* does it cause damage. This dog still needed calcium in the diet for healthy bones and teeth.

## CONCLUSION

With treatment this dog regained a functional degree of vision and resolution in associated signs of adrenal excess. Whether this stemmed from prompt veterinary care, a comprehensive approach to treatment, or both remains unclear. Since photoreceptor cell death is not immediate in SARD, owners should be encouraged to pursue prompt estrogen/sex hormone testing and a comprehensive approach to both adrenal and retinal issues.

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