SARDS case report #9

IVIg therapy does not prevent adrenal exhaustion in a dog with Sudden Acquired Retinal Degeneration

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ABSTRACT

Purpose. To describe the treatments, clinical presentation, and laboratory findings of one dog affected with Sudden Acquired Retinal Degeneration (SARD). **Method** and **Results.** Animal studied: a nine-year-old intact male Soft Coated Wheaton Terrier with clinical signs of sudden onset blindness, confusion, lethargy, aggression, circling/pacing, ataxia, anorexia, and olfactory loss. *Part I.* The veterinary ophthalmologist diagnosed Sudden Acquired Retinal Degeneration (SARD) and prescribed IVIg therapy. No improvement in visual acuity was reported. *Part II.* The general practice veterinarian diagnosed hypothyroidism and prescribed levothyroxine. Signs of aggression resolved. Lethargy improved initially but worsened in subsequent months along with escalating confusion, circling/pacing, ataxia, anorexia, weight loss, and olfactory loss. *Part III.* An endocrine and immunology (E&I) panel ten months post-onset revealed adrenal exhaustion via elevated adrenal sex-hormone levels (total estrogen). Cortisol replacement therapy was initiated both PO and IM. Repeat E&I panel demonstrated improvement in all parameters. Owners reported improvement in 88% of clinical signs. **Conclusion**. This SARD-affected dog developed adrenal exhaustion despite IVIg therapy at SARD-onset. Dogs should be screened for adrenal exhaustion at the time of SARD diagnosis.

SUMMARY in plain English

At the time of vision loss this dog was confused, tired, and aggressive. He favored his left hind leg and his head listed to the right. He had little appetite.

He was treated first with injectable immunoglobulin (IVIg) therapy — an experimental treatment for SARD. It did not improve vision or other symptoms.

The dog was also diagnosed with low thyroid levels shortly thereafter and was started on thyroid hormone. At first, the dog was more energetic but as the months wore on he became increasingly tired and confused. Circling/pacing and loss of appetite worsened. He lost his ability to smell.

An E&I panel indicated the dog had adrenal exhaustion. He was treated with cortisol replacement therapy. Two months later there was improvement in all levels of hormones, immunoglobulins, and nearly all clinical signs/symptoms.

Conclusion: IVIg therapy did not prevent this dog from developing advanced adrenal exhaustion.

DESCRIPTION OF THE CASE

A nine-year-old intact male Soft Coated Wheaton Terrier developed sudden onset blindness, confusion, lethargy, aggression, circling/pacing, ataxia, and anorexia. Weight at SARD onset = 48 pounds. The dog had a history of skin allergies and hot spots.

METHODS AND RESULTS

Part I. The veterinary ophthalmologist diagnosed Sudden Acquired Retinal Degeneration (SARD) via ERG and prescribed IVIg therapy: Gammaguard 10gm IV, day one and day three. No improvement in vision was reported.

Part II. Additional diagnostics performed at SARD-onset revealed T4 below normal. (table 1) The general practice veterinarian initially prescribed levothyroxine 0.3mg PO BID, later modified to 0.3mg PO a.m. and 0.15mg PO p.m.

Table 1. T4 Immunoassay (Antech Diagnostics)

	Initial	Normal range
T4	0.8 ug/dL	1.6-5.0 ug/dL

Signs of aggression resolved with thyroid hormone replacement. Lethargy improved initially but worsened in subsequent months along with escalating confusion, circling/pacing, ataxia, and significant anorexia. The dog experienced continued weight loss and olfactory loss. Ten months post SARD-onset bodyweight = 35 pounds (13-pound loss from onset). The owners stated, “The dog’s appetite is almost non-existent. We have to feed him by hand. Inside the house he paces most of the time. Once outside, he can’t find his way back in and will circle until we stop him.”

Part III. An endocrine and immunology (E&I) panel (National Veterinary Diagnostic Services, Quail Valley, CA) ten months post-SARD onset revealed adrenal exhaustion evidenced by elevated total estrogen, low serum immunoglobulins (IgA and IgM), low T3 and low T4. (table 2) “Cortisol” level appeared elevated.

ataxia = irregular muscle action, loss of coordination

anorexia = loss of appetite

IVIg therapy is a recently proposed treatment for SARD that consists of injecting human immunoglobulins into these dogs. Immunoglobulins are akin to “soldiers” of the immune system. IVIg therapy is based on the idea that SARD is an autoimmune disease and that injecting these dogs with immunoglobulins stops the autoimmune attack on the retina. (The theory of SARD as an autoimmune disease is more fully addressed on page 3.)

Thyroid treatment was also started shortly after blindness. Thyroid improved a few of the dog’s clinical signs/symptoms, but soon the dog continued to decline.

Ten months later the dog was diagnosed with advanced adrenal exhaustion. This means the adrenal glands could no longer make *useable* cortisol and consequently made too much adrenal estrogen instead.

Table 2. Endocrine/Immune panel (NVDS)

	Initial	3-mo	Normal range
Total estrogen	25.09	25.07	20.00-25.00pg/L
Cortisol	2.85	1.54	1.00-2.50 ug/dL
T3	51.06	83.31	100.00-200.00 ng/dL
T4	0.82	1.84	2.00-4.50 ug/dL
IgA	53	59	70-170 mg/dL
IgG	1116	1168	1000-2000 mg/dL
IgM	92	97	100-200 mg/dL

The initial "cortisol" value appeared high on the lab results but this reading can often be the sum total of several hormones. This is discussed in greater detail on page 7. Immunoglobulins in the bloodstream (serum) were generally below normal. This is a common finding when estrogen is elevated.

Low-dose cortisol replacement therapy was initiated both IM (dexamethasone sodium phosphate 1.6mg, single dose; triamcinolone acetonide 0.12mg, single dose), and PO (methylprednisolone 3mg PO SID day three). Clinical signs showed little improvement after three weeks and more aggressive treatment was initiated. Oral methylprednisolone was replaced by weekly injections of dexamethasone sodium phosphate 1.6mg IM; triamcinolone acetonide 0.12mg IM.

The dog was started on low-dose cortisol replacement (medrol tablets). After three weeks of treatment the dog was still struggling with his lethargy, confusion, etc., so treatment was ramped-up a notch. Cortisol was supplied by weekly injections rather than tablets. Injectable cortisol is absorbed into the body more easily than tablets, especially when dogs are very sick.

After four weeks the owner reported improvement in 88% of remaining signs stating that, "His appetite improved to where we no longer have to hand-feed him. His tail is up more and his cognitive abilities have improved especially right after the injections when he'll come directly to the sound of my voice. He's circling and pacing less, and one day he was even sniffing around. He hadn't done that in about six months." Bodyweight = 37.5 pounds. No improvement in vision was reported. Repeat E&I panel indicated improvement in all parameters. Both elevated estrogen and elevated "cortisol" declined with cortisol falling within normal range. (table 2)

DISCUSSION

Researchers have proposed various models to explain the etiology of SARD, including excitotoxicity (1), apoptosis (2), adrenal exhaustion (3-5) and autoimmune activity (6-10).

Over the years, a number of theories have been put forth to explain the cause of SARD. These include excitoxicity (a "seizure" of the retina), apoptosis (a self-destruct message within the retina), adrenal exhaustion (elevated sex-hormones that trigger multiple health problems including seizures), and finally, autoimmune disease (when the body attacks its own tissues).

Autoimmune model of SARD

SARD demonstrates some similarities to immune-mediated retinopathies in humans, which lead researchers to reexamine autoimmune activity as a possible etiology for SARD. Human

immune-mediated retinopathies respond favorably to intravenous immunoglobulin (IVIg) therapy. (11) Some SARD-affected dogs also demonstrate the presence of autoantibodies and IVIg therapy has improved functional vision in some cases. These findings led some researchers to categorize SARD as an immune-mediated condition. (9) This conclusion is not a consensus within the veterinary community. (7,8)

The autoantibodies identified in SARD-affected dogs are antibodies specific to neuron-specific enolase (NSE), a protein enzyme normally found within neural and retinal cells. (12) NSE is released when cells are damaged or destroyed via apoptosis. (13) Researchers now question whether autoantibodies associated with SARD are the result of retinal destruction rather than a causative factor. (10)

Additionally, the autoimmune model does not sufficiently explain the adrenal sex-hormone production reported in these dogs. Proponents of the autoimmune model suggest that the retina's reduced light sensitivity results in a loss of circadian-regulated hormonal activity. (9) Dogs with other forms of complete, sudden-onset blindness resulting from head trauma, hypoxia, optic neuritis, end-stage glaucoma or bilateral enucleation do not routinely develop signs of adrenal excess (PU/PD/PP, confusion, depression, lethargy, etc.) as reported in SARD-affected dogs.

Adrenal exhaustion model of SARD

In contrast, this author proposes an endocrine model for the etiology of SARD, which originates with adrenal exhaustion and culminates with photoreceptor excitotoxicity and cell death. Dogs affected with SARD routinely present with signs suggestive of hypercortisolism (14-18) but only a minority are diagnosed with Cushing's disease. (15,19) Early on, researchers speculated that signs of hypercortisolism were the physiological response to some unidentified stress (18). SARD-affected dogs also demonstrate elevated levels of adrenal sex hormones (androstenedione, estradiol, progesterones, and testosterone) within the first year of blindness. (4,20,21) One explanation for this pattern of events is Selye's model of stress adaptation, which describes the progression from adrenal gland hyperactivity to adrenal gland exhaustion (cortisol insufficiency). In Selye's model, adrenal activity is marked by three phases: alarm, resistance, and exhaustion. (22)

Humans develop autoimmune diseases of the retina that result in sudden vision loss. Immunoglobulin injections (IVIg) have had a positive result in some cases, so this treatment was tried in SARD dogs. Some dogs treated with IVIg also show improved vision and these researchers concluded that SARD is an autoimmune disease.

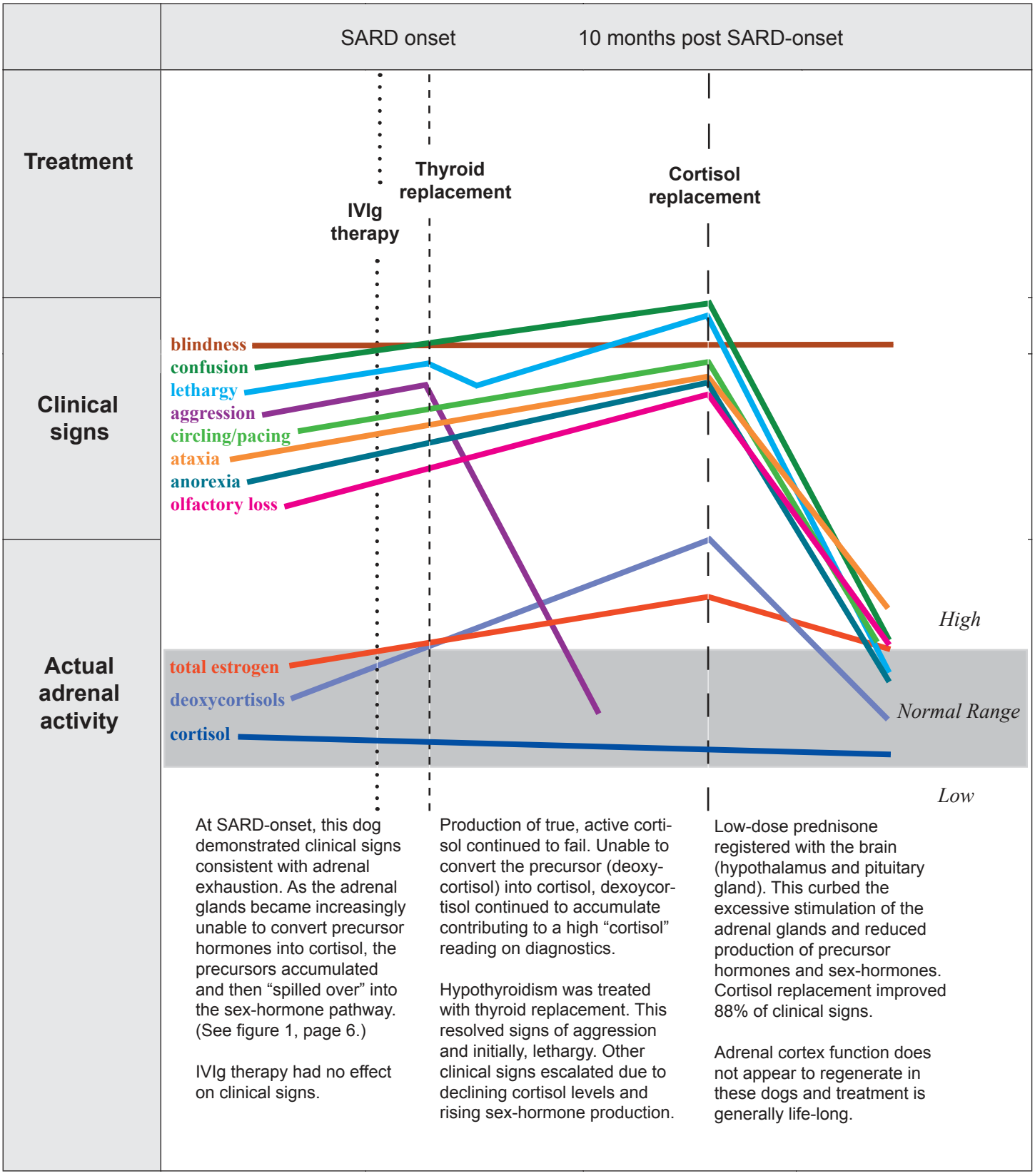
Other researchers have concluded that SARD is not an autoimmune disease. Their research shows that the molecules thought to trigger autoimmune activity may actually be *the result of* the retinal cell destruction, rather than *the cause*.

The autoimmune concept does not explain all of the other health problems that routinely plague SARD dogs. Lots of other dogs go blind suddenly that don't develop the kinds of health problems well-known in SARD dogs. These other health problems indicate that there is a deeper problem in SARD dogs—an adrenal gland problem.

This author provides a different explanation for the cause of SARD. It starts with an adrenal gland problem — failure to make good, useable cortisol (the antiinflammatory hormone). This causes a rise in adrenal estrogen production. High levels of estrogen cause the retinal/nerve cells to have a "Charlie horse" or "seizure". This can damage the retinal cells. The body clears away the damaged cells after a few months.

Nearly all of the research that has been done over the past thirty years is explained by **adrenal exhaustion** model of SARD.

Table 3. Case overview



Phases of adrenal activity

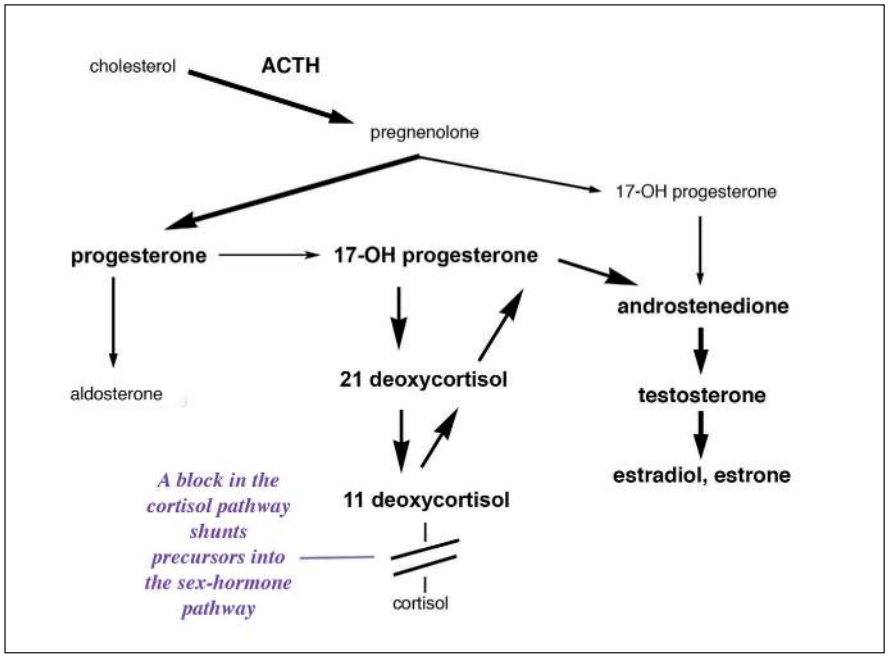
During the alarm phase the body responds to stressors with increased hypothalamic-pituitary-adrenal (HPA) activity and cortisol secretion. Cortisol production returns to normal when the stressor is resolved. This is the normal, healthy response to psychological and physical stressors (irritation).

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. (23)

In the final phase—exhaustion—the adrenal glands are unable to sustain elevated cortisol production. (24) The enzyme 11β-hydroxylase fails to convert deoxycortisol to cortisol. Consequently, precursor hormones such as deoxycortisol, progesterone, and 17-OH-progesterone accumulate. These precursors are rerouted into the adjacent sex-hormone pathway increasing production of androstenedione, testosterone, and estradiol. (25-27) (figure 1)

90%-98% of SARD-affected dogs test positive for adrenal exhaustion. (20,28) This scenario has also been described as: hyperestrogenism, adrenal hyperplasia-like syndrome, atypical Cushing's disease (if sex hormones are assayed) or atypical Addison's disease (if cortisol and aldosterone are assayed). Humans born with a similar group of conditions are described as having congenital adrenal hyperplasia (CAH).

Figure 1. Sex-hormone accumulation during adrenal exhaustion



When the adrenal glands are healthy they respond to stress/irritation by producing hormones like cortisol and adrenalin. When the stress is over, the hormones return to their normal levels.

If stress/irritation is chronic, the adrenal glands get stuck in "overdrive" or the resistance phase. They continuously pump out slightly excessive amounts of cortisol.

Eventually, the adrenal glands become exhausted from this. When they can no longer produce cortisol, the precursors hormones (the building blocks of cortisol) pile up like water behind a dam. These precursors then spill over into the next pathway—the sex-hormone pathway. Levels of adrenal sex-hormones, including estrogen, rise above normal.

This author originally believed that SARD dogs experienced the overdrive phase when they went blind. More recent information suggests that this is not the case. The vast majority (98%) of SARD dogs experience adrenal *exhaustion* when they go blind. In other words, these dogs produce *too little cortisol* and too much estrogen. The high levels of estrogen *mimic* Cushing's disease.

Clinical presentation of adrenal exhaustion

Hyperestrogenism produces effects similar to hypercortisolism including, confusion, fatigue, depression, irritability, agitation, pancreatitis, embolisms, and seizures in humans; (29-35) renal disease, and bone marrow depression in dogs (36,37); systemic immunoglobulin suppression, hepatic dysfunction, increased mast cell activity, and thyroid binding in both species. (32,38-41) Estrogen-treated rats experience PU/PD and an inability to concentrate urine. (42,43)

Excitotoxicity

Estrogen can exhibit seemingly contradictory effects in the body. Estrogen is neuroprotective at low levels and neurocytotoxic at high levels, the latter resulting in excitotoxicity and increased intracellular calcium concentrations. (44) Excessive calcium influx leads to hyperpolarization and mitochondrial damage. (45) In turn, mitochondrial damage signals apoptosis or programmed cell death. Excitotoxicity has been previously identified as a plausible mechanism in SARD. (1) Immunoglobulins regulate multiple physiological functions including influx of intracellular calcium (46-48), which may explain the positive effects of IVIg therapy in some SARD cases.

Apoptosis

Apoptosis has also been identified as a mechanism present in SARD. (2) During apoptosis, mitochondrial DNA is fragmented, the cell is turned “inside out” and a variety of proteins (including neuron-specific enolase) are exposed on the membrane surface. This signals phagocytic cells such as macrophages to remove cell fragments. In situations of extensive cell death, macrophages become overwhelmed by large numbers of apoptotic cells and cannot efficiently clear them from the area. (49) Prolonged antigen presentation can result in activation of T-cells and autoimmune sensitivity. (50) Elevating levels of estrogen has been shown to increase the number of autoreactive immunoglobulin-secreting B-cells in the peripheral immune system. (51)

As two molecules go, cortisol and estrogen are *quite* similar and can have many of the same effects on the body. This is why dogs with elevated estrogen can *appear* to have Cushing’s disease even though they test negative for it.

embolism = blood clot (ie. a stroke)
renal disease = kidney failure
hepatic dysfunction = liver disease
PU/PD = increased drinking and urination

High levels of estrogen permit excess calcium to enter nerve/retinal cells. This excess calcium damages the tiny organs inside the cells. After 3-4 months the body recognizes the damage and starts to destroy the retinal cells.

There are basically two ways that the body destroys a cell. One is a self-destruct message called apoptosis. The other is through autoimmune destruction. These are two distinct and differing methods.

During apoptosis the cells are turned inside out and the debris is cleared away. There is normally no inflammation when cells are destroyed by apoptosis.

During autoimmune destruction the immune system attacks the body’s own cells and destroys them through an inflammatory response. The autoimmune response has recently gained attention as a possible cause of SARD, however apoptosis was identified as the method of destruction in SARD as early as 1998. Apoptosis can *lead to* events in the body that look like autoimmune disease.

So, if SARD is not an autoimmune disease, why would some SARD-dogs improve with IVIg therapy? IVIg therapy may be reducing the amount of calcium allowed to enter the retinal cells.

Adrenal exhaustion increases production of related adrenal sex-hormones, such as progesterone, androstenedione, and testosterone leading to heat intolerance, acne, obesity, and hirsutism. (27,52) Concentrations of these hormones have also been shown to stimulate antigen presentation. (51)

In advanced adrenal exhaustion, inadequate cortisol production may ultimately result in *anorexia*, abdominal pain, *weight loss*, vomiting, diarrhea or bowel incontinence, and *weakness*. Without treatment, severe hypocortisolism is fatal. (53,54)

Interpretation of cortisol values

The dog described here demonstrated elevated cortisol values initially and a normal cortisol value after three months of low-dose cortisol replacement therapy. This seems counterintuitive but can be explained with a brief review of molecular biology and steroidogenesis.

Chronic activation of the HPA axis (stress or physical irritation) acts to increase the production of hormone stereoisomers—molecules possessing identical constituents, but differing in their three-dimensional arrangement. The isomer of cortisol most often described in the literature is 11-epicortisol. This isomer is less potent and does not exert activity equivalent to cortisol, including regulatory activity on the HPA axis. (55-58)

Few diagnostic tests differentiate cortisol from cortisol isomers. Therefore, a “cortisol” value may be an amalgamation of active cortisol plus less active stereoisomers. Patients producing high levels of stereoisomers and low levels of normal cortisol may demonstrate a normal or high “cortisol” value on diagnostic tests.

As adrenal exhaustion advances, deoxycortisol levels accumulate due to the impasse in the cortisol pathway. (figure 1) Few diagnostic tests distinguish between cortisol and deoxycortisol. Consequently, deoxycortisol may be erroneously read as part of the “cortisol” value, as well. (59-61)

Low cortisol production also raises other adrenal sex-hormone levels in addition to estrogen. The results include excessive panting, flesh-colored pimples, weight gain, and heavy coat growth. Elevated sex-hormones can cause events in the body that look like autoimmune disease.

Unlike most SARD-dogs, this dog had almost no appetite prior to treatment. This indicates he was experiencing advanced adrenal exhaustion, which can be fatal.

Readers may question why this dog was given cortisol replacement when his intitial cortisol result was *high*. The realty is, all laboratory tests have their limits of accuracy and this one is a good example:

When the adrenal gland can not make sufficient cortisol the tissues of the body try to increase cortisol levels by converting stored cortisone into active cortisol. Unfortunately this can lead to the production of molecules that are “backwards” or “mirror image molecules” of cortisol. These molecules are weak (“biologically inactive”) and don’t do the work of real cortisol. However, they can be picked up by many lab tests and be counted in the cortisol total.

Furthermore, when the adrenal gland can not make sufficient cortisol the precursors or building blocks pile up. The direct precursor to corisol is called deoxycortisol. Many lab tests can pick up this hormone and count it as “cortisol” because the molecules are too similar for the tests to tell apart.

So the high “cortisol” reading in this dog was really a combination of deoxycortisol (the precursor) as well as epicortisol (the mirror image molecule).

Effects of low-dose prednisone

Oral prednisone is well known to exert regulatory control over the HPA axis. In cases of adrenal exhaustion, cortisol replacement normalizes ACTH secretion, which reduces excessive levels of deoxycortisol and perhaps 11-epicortisol. As a result of replacement therapy, "cortisol" values that were erroneously elevated fall to their true value. (24,62) The practitioner must be suspect in cases when *both* sex-hormones and cortisol levels appear elevated, because it is inadequate cortisol production that has long been reported as a primary cause of elevated adrenal sex-hormones in both man and dog. (4,25,26,38,63)

CONCLUSION

This case supports the adrenal exhaustion model of SARD. IVIg therapy did not prevent this dog from developing advanced adrenal exhaustion. Practitioners should encourage owners to pursue prompt screening and treatment for adrenal exhaustion at SARD-onset. Recommendations for future research include calcium channel blocking therapies in conjunction with hormone replacement and antioxidant therapies.

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When cortisol replacement is supplied by pills or injections, the brain stops stimulating the adrenal glands to try and make cortisol. When the adrenal glands relax, the levels of precursors (deoxycortisol and sex-hormones) drop. Levels of epicortisol likely drop, too. When the patient is retested, the cortisol levels reflect the true level of cortisol production (low or low-normal). The primary reason for high sex-hormone production is *low cortisol production.*

To review, the bulk of research suggests that SARD is basically an adrenal gland problem that progresses like this:

• The adrenal gland stops making sufficient cortisol and adrenal sex-hormones (estrogen) rise.

• Estrogen permits excessive calcium to enter retinal cells.

• Excessive calcium causes a "seizure" or "Charley horse" of the retina (resulting in sudden vision loss) and gradually damages the retinal cells.

• After 3-4 months of damage the body triggers apoptosis and destroys the damaged retinal cells.

• Low cortisol and high sex-hormone levels go on to cause multiple other health problems in these dogs.

Dogs should be screened and treated for adrenal exhaustion at the time of SARD diagnoses. This may prevent months or years of poor health and distress.

REFERENCES

1. Abrams KL, Dreyer EB, Riis R. Excitotoxicity in Canine Sudden Acquired Retinal Degeneration Syndrome (abstract). *26th Annual Meeting of the College of Veterinary Ophthalmologists* 1995; **26**: 39.

2. Miller PE, Galbreath EJ, Kehren JC, Steinberg H, Dubielzig RR. Photoreceptor cell death by apoptosis in dogs with Sudden Acquired Retinal Degeneration syndrome (abstract). *American Journal of Veterinary Research* 1998; **59**: 149-152.

3. Levin C. Environmental factors and signs of hypercortisolism in dogs affected with Sudden Acquired Retinal Degeneration (SARD). *Journal of the American Holistic Veterinary Medical Association* 2006; **24**: 11-19.

4. Levin C. Sudden Acquired Retinal Degeneration, associated pattern of adrenal activity, and hormone replacement in three dogs – a retrospective study. *Proceedings of the 38th Annual Meeting of the College of Veterinary Ophthalmologists* 2007; **38**: 32.

5. Levin C. Sudden Acquired Retinal Degeneration, associated pattern of adrenal activity, and hormone replacement in a Brittany Spaniel – case report. *Proceedings of the 38th Annual Meeting of the College of Veterinary Ophthalmologists* 2007; **38**: 33.

6. Bellhorn RW, Murphy CJ, Thirkill CE. Anti-retinal immunoglobulins in canine ocular disease (abstract). *Seminars in Veterinary Medicine and Surgery (Small Animal)* 1988; **3**: 28-32.

7. Gilmour MA, Cardenas MR, Blaik MA, Bahr RJ, McGinnis JF. Evaluation of a comparative pathogenesis between cancer-associated retinopathy in humans and sudden acquired retinal degeneration syndrome in dogs via diagnostic imaging and western blot analysis. *American Journal of Veterinary Research* 2006; **67**: 877-881.

8. Keller RL, Kania SA, Hendrix DVH, Ward DA, Abrams K. Evaluation of canine serum for the presence of antiretinal autoantibodies in sudden acquired retinal degeneration syndrome (abstract). *Veterinary Ophthalmology* 2006; **9**: 195-200.

9. Grozdanic SD, Harper MM, Kecova H. Antibody-mediated retinopathies in Canine Patients: Mechanisms, Diagnosis, and Treatment Modalities. *Veterinary Clinics, Small Animal* 2008; **38**: 361-387.

10. Braus BK, Hauck SM, Amann B, Heinrich C, Fritsche J, Kostlin R, Deeg CA. Neuron-specific enolase antibodies in patients with sudden acquired retinal degeneration syndrome (abstract). *Veterinary Immunology and Immunopathology* 2008; **124**: 177-183.

11. Guy J, Aptsiauri N. Treatment of paraneoplastic visual loss with intravenous immunoglobulin: Report of 3 cases. *Archives of Ophthalmology* 1999; **17**: 471-7.

12. Rich KA, Zhan Y, Blanks JC. Migration of cone photoreceptors in the developing mouse retina (abstract). *Journal of Comparative Neurology* 1997: **388**: 47-63.

13. Berger RP, Pierce MC, Wisniewski SR, Adelson PD, Clark RS, Ruppel RA, Kochanek PM. Neuron-specific enolase and S100B in cerebrospinal fluid after severe traumatic brain injury in infants and children (abstract). *Pediatrics* 2002; **109**: E31.

14. Acland GM, Irby NL, Aguirre GD, Gross S, Nitray SF, Notarfrancesco K. Sudden acquired retinal degeneration in the dog: clinical and morphologic characterizations of the “silent retina” syndrome. *15th Annual Meeting of the College of Veterinary Ophthalmologists* 1984; **15**: 86-104.

15. van der Woerdt A, Nasisse MP, Davidson MG. Sudden Acquired Retinal Degeneration in the dog: clinical findings in 36 cases. *Progress in Comparative Ophthalmology* 1991; **1**: 11-18.

16. Vainisi SJ, Schmidt, GM, West CS, Anderson R, Herrmann H, Ketring K, Font RL. Metabolic toxic retinopathy preliminary report. *14th Annual Meeting of the College of Veterinary Ophthalmologists* 1983; **14:** 76-81.

17. Abrams KL, Gareen LF, Marchand KN. Factors associated with canine Sudden Acquired Retinal Degeneration Syndrome (SARDS): 350 cases (abstract). *32nd Annual Meeting of the College of Veterinary Ophthalmologists* 2001; **32**: 11.

18. Acland GM, Aguirre GD. Sudden Acquired Retinal Degeneration: clinical signs and diagnosis. *17th Annual Meeting of the College of Veterinary Ophthalmologists* 1986; **17**: 58-63.

19. Holt E, Feldman EC, Buyukmihci NC. The prevalence of hyperadrenocorticism (Cushing's syndrome) in dogs with sudden acquired retinal degeneration (SARD) (abstract). *30th Annual Meeting of the College of Veterinary Ophthalmologists* 1999; **30**: 35.

20. Carter RT, Bentley E, Oliver JW, Miller PE, Herring IP. Elevations in Adrenal Sex Hormones in Canine Sudden Acquired Retinal Degeneration Syndrome (SARDS) (abstract). *34th Annual Meeting of the College of Veterinary Ophthalmologists* 2003; **34**: 40.

21. Personal correspondence with E. Bentley DVM, June 3, 2005.

22. Selye H. *The Stress of Life* revised edition. McGraw-Hill, Incorporated: New York, 1976.

23. Young EA, Vasquez D. Hypercortisolemia, hippocampal glucocorticoid receptors, and fast feedback (abstract). *Molecular Psychiatry* 1996; **1**: 149-159.

24. Jeffries MK. *Safe Uses of Cortisol* third edition. Charles C. Thomas Publisher, Ltd, Springfield, 2004.

25, Guthrie GP, Wilson EA, Quillen DL, Jawad MJ. Adrenal androgen excess and defective 11-beta-hydroxylation in women with idiopathic hirsutism (abstract). *Archives of Internal Medicine* 1982; **142**: 729- 735.

26, Deaton M, Glorioso JE, Mclean DB. Congenital Adrenal Hyperplasia—Not really a zebra. *American Family Physician* 1999; **59**: 1190-1196.

27, Derman RJ. Effects of sex steroids on women's health: implications for practitioners (abstract). *American Journal of Medicine* 1995; **1A**: 137S-143S.

28. Levin C. Adrenal exhaustion and immunoglobulin suppression: Common findings in 53 dogs affected with Sudden Acquired Retinal Degeneration (SARD). Unpublished data: *www.petcarebooks.com/pdf/SARDS_09.pdf* January 2009.

29. Sohrabji F. Estrogen: a neuroprotective or proinflammatory hormone? Emerging evidence from reproductive aging models (abstract). *Annals of the New York Academy of Sciences* 2005; **1052**: 75-90.

30. Bush TL. The adverse effects of hormonal therapy (abstract). *Cardiology Clinics* 1986; **4**: 145-152.

31. Bagshaw S. The combined oral contraceptive. Risks and adverse effects in perspective (abstract). *Drug Safety* 1995; **12**: 91-96.

32. Rossi GV. Side-effects and possible complications of oral contraceptive drugs (abstract). *American Journal of Pharmacology* 1966, **138**: 127-136.

33. Foldvary-Schaefer N, Harden C, Herzog A, Falcone T. Hormones and seizures (abstract). *Cleveland Clinical Journal of Medicine* 2004; **71**: 11S-18S.

34. Goldenberg N, Wang P, Glueck CJ. An observational study of severe hypertriglyceridemia, hypertriglyceridemic acute pancreatitis, and failure of triglyceride-lowering therapy when estrogens are given to women with and without familial hypertriglyceridemia (abstract). *Clinica Chimica Act: International Journal of Clinical Chemistry* 2003; **332**; 11-19.

35. Parker WA. Estrogen-induced pancreatitis (abstract). *Clinical Pharmacy* 1983; **2**: 75-79.

36. Hart JE. Endocrine pathology of estrogens: species differences (abstract). *Pharmacology Therapeutics* 1990; **47**: 203-218.

37. Zayed I, van Esch E, McConnell RF. Systemic and histopathologic changes in beagle dogs after chronic daily oral administration of synthetic (ethinyl estradiol) or natural (estradiol) estrogens, with special reference to the kidney and thyroid (abstract). *Toxicologic Pathology* 1998; **26**: 730-741.

38. Plechner AJ. Cortisol abnormality as a cause of elevated estrogen and immune destabilization: Insights for human medicine from a veterinary perspective. *Medical Hypothesis* 2004; **62**: 575-581.

39. Vasiadi M, Kempuraj D, Boucher W, Kalogeroitros D, Theoharides TC. Progesterone inhibits mast cell secretion (abstract). *International Journal of Immunopathology and Pharmacology* 2006; **19**: 787-794.

40. Blum M, Zacharovich D, Pery J, Kitai E. Lowering effect of estrogen replacement treatment on immunoglobulins in menopausal women (abstract). *Revue française degynecologie et d'obstetrique* 1990; **4**: 207-209.

41. Marik PE. Adrenal-exhaustion syndrome in patients with liver disease (abstract). *Intensive Care Medicine* 2006; **32**: 275-280.

42. Carlberg KA, Fregly MJ, Fahey M. Effects of chronic estrogen treatment on water exchange in rats (abstract). *American Journal of Physiology–Endocrinology and Metabolism* 1984; **247**: E101-E110.

43. Longhurst PA, Kauer J, Leggett RE, Levin RM. The influence of ovariectomy and estradiol replacement on urinary bladder function in rats (abstract). *Journal of Urology* 1992; **148**: 915-919.

44. Chen S, Nilsen J, Brinton RD. Dose and Temporal Pattern of Estrogen Exposure Determines Neuroprotective Outcome in Hippocampal Neurons: Therapeutic Implications (abstract). *Endocrinology* 2006; **147**: 5303-5313.

45. He L, Poblenz AT, Medrano CJ, Fox DA. Lead and Calcium Produce Rod Photoreceptor Cell Apoptosis by Opening the Mitochondrial Permeability Transition Pore (abstract). *Journal of Biology and Chemistry* 2000; **275**: 12175-12184.

46. Rendu E, David-Dufilho M, Schussler O, Pernolet MG, Brunet A, Le Quan Sang KH. Intravenous immunoglobulins G modulate calcium signals, von Willebrand factor secretion and nitric oxide metabolism in human endothelial cells (abstract). *XIX Annual Congress of the International Society of Thrombosis and Haemostasis* 2003; **1:** P0151.

47. Kondo N, Kasahara K, Kameyama T, Suzyki Y, Shimozawa N, Tomatsu S, Nakashima Y, Hori T, Yamagaishi A, Watanabe K, Haga M, Orii T. Intravenous immunoglobulins suppress immunoglobulin productions by suppressing Ca2+ -dependant signal transduction through Fc receptors in B lymphocytes (abstract). *Scandinavian Journal of Immunology* 2006; **40**: 37-42.

48. Basta M, Van Goor F, Luccioli S, Billings EM, Vortmeyer AO, Baranyi L, Szebeni J, Alving CR, Carroll MC, Berkower I, Stojilkovic SS, Metcalfe DD. $F(ab)'_2$ –mediated neutralization of C3a and C5a anaphylatoxins: a novel effector function of immunoglobulins (abstract). *Nature Medicine* 2003; **9**: 431-438.

49. Huggins ML, Todd I, Cavers MA, Pavuluri SR, Tighe PJ, Powell RJ. Antibodies from systemic lupis erythmatosus (SLE) sera define differential release of autoantigens from cell lines undergoing apoptosis (abstract). *Clinical and Experimental Immunology* 1999; **118**: 322-328.

50. Hall JC, Casciola-Rosen L, Rosen A. Altered structure of autoantigens during apoptosis (abstract). *Rheumatic Disease Clinics of North America*; **30**: 455-471.

51. Conn PM, Freeman ME. *Neuroendocrinology in Physiology and Medicine*. Humana Press, Clifton, New Jersey, 1999.

52. Landau RL, Poulos JT. The metabolic influence of progestins (abstract). *Advances in Metabolic Disorders* 1971; **5:** 119-147.

53. Felman EC, Nelson RW. *Canine and Feline Endocrinology and Reproduction*, Third edition. Saunders, St. Louis, 2004.

54. Wilson W. Preventing a fatal outcome in Addison's disease. *Journal of the Academy of Physician's Assistants* 2004; **17**: 35-38.

55. Bayarri VM, Sancho S, Campos R, Faus R, Simon JM, Porcar E, Tormo C, Hernandez A. The euthyroid sick syndrome in severe acute illness (abstract). *Presse Medical* 2007; **36**: 1550-1556.

56. Resetic J, Reiner Z, Ludecke D, Riznar-Resetic V, Sekso M. The effects of cortisol, 11-epicortisol, and lysine vasopressin on DNA and RNA synthesis in isolated human adrenocorticotropic hormone-secreting pituitary tumor cells (abstract). *Steroids* 1990; **55**: 98-100.

57. Beckford U, Holmes M, Gillham B, Jones M. Biphasic inhibition of bioactive hypothalamic corticotrophin releasing factor secretion in vitro by corticosterone and prevention of the second phase by various steroids (abstract). *Journal of Endocrinology* 1983; **97**: 339-346.

58. Nicholson S, Mahmoud S, Sutanto W, Gillham B, Jones M. The Combination of 17-Hydroxyprogesterone and 11-Epicortisol Prevents the Delayed Feedback Effect of Natural and Synthetic Glucocorticoids (abstract). *Neuroendocrinology* 1986; **43**: 491-497.

59. Thomasson B, Steenburg W. Plasma clearance of cortisol and 11-deoxycortisol in dogs (abstract). *American Journal of Physiology*; 1965: 84-89.

60. Cohen J, Ward G, Prins J, Jones M, Venkatesh B. Variability of cortisol assays can confound the diagnosis of adrenal insufficiency in the critically ill population (abstract). *Intensive Care Medicine*; **32**: 1901-1905.

61. Oh TH, Han HR, Park HM. Determination of urinary cortisol-creatinine ratios by sequential thin layer chromatography and ELISA in dogs (abstract). *Journal of the Korean Society of Veterinary Science* 1999; **39:** 1006-10012.

62. Levin C. Concurrent elevations in cortisol and total estrogen in a dog affected with Sudden Acquired Retinal Degeneration Syndrome (SARDS). www.petcarebooks.com/pdf/CaseReport5.pdf, 2007; and pending publication in *Dogs, Diet, and Disease: An Owner's Guide to Diabetes Mellitus, Pancreatitis, Cushing's Disease and More*, Second edition. Lantern Publications, Oregon City.

63. Naessen S, Carlstrom K, Garoff L, Glant R, Hirschberg AL. Polycystic ovary syndrome in bulimic women–an evaluation based on new diagnostic criteria (abstract). *Gynecological Endocrinology* 2002; **22**:388-394.