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Sudden Acquired Retinal Degeneration, associated pattern of adrenal activity, and hormone replacement therapy in a Brittany Spaniel

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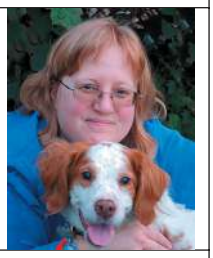
ABSTRACT

Purpose. To describe the clinical and laboratory findings, hormone replacement therapy, and outcome of one dog affected with Sudden Acquired Retinal Degeneration (SARD). **Methods.** Animal studied: a nine-year-old neutered male Brittany Spaniel with escalating signs of lethargy, confusion, agitation, seizures, head tics, anorexia, and GI distress. Time interval from SARD onset = 3 years. The general practice veterinarian ordered an abdominal U/S and ACTH-suppression test (University of Illinois, College of Veterinary Medicine, Urbana, IL), which were negative for Cushing's disease. An endocrine/immune (E&I) panel (National Veterinary Diagnostic Services, Quail Valley, CA) identified low levels of immunoglobulins (IgA, IgG and IgM), low cortisol and elevated estrogen. T3 and T4 fell within the bottom 23% of normal range. The general practice veterinarian initiated hormone replacement with low-dose injectable glucocorticoids including dexamethasone sodium phosphate (IVX Animal Health, St. Joseph, MO) and triamcinolone acetonide (Bristol-Myers Squibb, Princeton, NJ) followed by low-dose oral methylprednisolone (Vintage Pharmaceuticals, Charlotte, NC) and levothyroxine (Lloyd, Inc., Shenandoah, IA). The E&I panel was repeated at three and six months. **Results**. The dog demonstrated a gradual shift toward normal immunoglobulin, estrogen and cortisol levels. T3 and T4 demonstrated a gradual rise toward the mid-normal range. The owner reported complete resolution in 62% of clinical adrenal signs and "some improvement" in an additional 38% at three months. By six months, 75% of clinical signs resolved. **Conclusion**. Three years after SARD onset, the dog described here demonstrated concurrent levels of elevated estrogen and low cortisol—a pathological pattern of steroidogenesis described as adrenal exhaustion. Low-dose glucocorticoid and thyroid hormone replacement had a significant positive effect on both clinical presentation and laboratory findings. The author provides a novel explanation for persistent clinical signs in a non-Cushingoid, SARD-affected dog.

DESCRIPTION OF THE CASE

This dog demonstrated fluctuating clinical signs suggestive of abnormal adrenal activity during the three-year period following SARD diagnosis. (table 1) As with many SARD-affected dogs, these problems resolved within the first year of blindness. By year three, however, lethargy returned. The dog also developed GI upset, including anorexia (loss of appetite), flatulence (gas), diarrhea, and emesis (vomiting). These episodes occurred several times per month, with the worst episode a week in duration. During these episodes, confusion, pacing, and agitation escalated. The dog developed frequent head tics, nystagmus (flickering eye movement), and ataxia (stumbling), which the owner described as seizures. The dog did not shed his coat that year and developed hirsutism (excess hair growth). A mast cell tumor was removed from the left rear leg.

Table 1. Clinical signs during three years post-SARD diagnosis

Clinical signs	**First** year post-SARD	**Second** year post-SARD	**Third** year post-SARD	**Fourth** year *hormone replacement*
				
polyphagia (appetite)	**X**	resolved		
obesity	**X**	resolved		
heat intolerance	**X**	resolved		
lethargy/depression	**X**	resolved	**X**	resolved 3 mo.
pacing/agitation			**X**	resolved 3 mo.
seizures			**X**	resolved 3 mo.
anorexia			**X**	resolved 3 mo.
hirsutism			**X**	resolved 3 mo.
confusion			**X**	resolved 6 mo.
head tics			**X**	improved 6 mo.
GI upset			**X**	improved 6 mo.

An ACTH suppression test and low-dose dexamethasone suppression test (University of Illinois, College of Veterinary Medicine, Urbana, IL) were performed in the first year post-SARD onset. Results were inconclusive for Cushing's disease. In year three an abdominal ultrasound and ACTH suppression test were negative for Cushing's disease.

An endocrinology and immunology (E&I) panel (National Veterinary Diagnostic Services, Quail Valley, CA) was also performed in year three, which identified elevated total estrogen, and low levels of cortisol and immunoglobulins. Thyroid levels (T3 and T4) fell within the bottom 23% of normal range. (tables 2 and 3)

Table 2. Endocrine diagnostic tests during three years post-SARD diagnosis

Diagnostics	**First** year post-SARD	**Second** year post-SARD	**Third** year post-SARD	**Fourth** year *hormone replacement*
ACTH-suppression	inconclusive		negative	
Low-dose dex.	negative			
Abdominal U/S			negative	
E&I panel			estrogen H cortisol L IgA L IgG L IgM L	Improvement in all parameters (see table 3)

METHODS

The general practice veterinarian initiated hormone replacement therapy to augment low cortisol and thyroid levels.

- dexamethasone sodium phosphate 3.6mg IM
- triamcinolone acetonide 0.3mg IM
- low-dose oral methylprednisolone 2mg PO sid
- levothyroxine 0.2mg PO bid
- Sulfasalazine 250mg PO BID 30" prior to other medications to improve intestinal absorption

The E&I panel was repeated at three and six months. Initial injections were repeated at four months in response to fluctuating anorexia and poor GI absorption.

RESULTS

Cortisol, estrogen, and immunoglobulin levels demonstrated a gradual shift toward the normal range. T3 and T4 gradually shifted toward mid-normal range. The owner reported complete resolution in 62% of adrenal signs and “some improvement” in 38% at three months. By six months, 75% of adrenal signs resolved.

Table 3. Results after hormone replacement

Hormone	Initial	3-month	6-month	Normal range
Cortisol	0.71	0.88	0.98	1.00-2.50 ug/dL
Total estrogen	25.15	25.07	25.03	20.00-25.00 pg/mL (males)
T3	110.09	115.73	121.16	100.00-200.00 ng/dL
T4	2.56	2.84	3.05	2.00-4.50 ug/dL
IgA	52	59	68	70-170 mg/dL
IgG	927	982	1,092	1,000-2,000 mg/dL
IgM	93	97	101	100-200 mg/dL

DISCUSSION

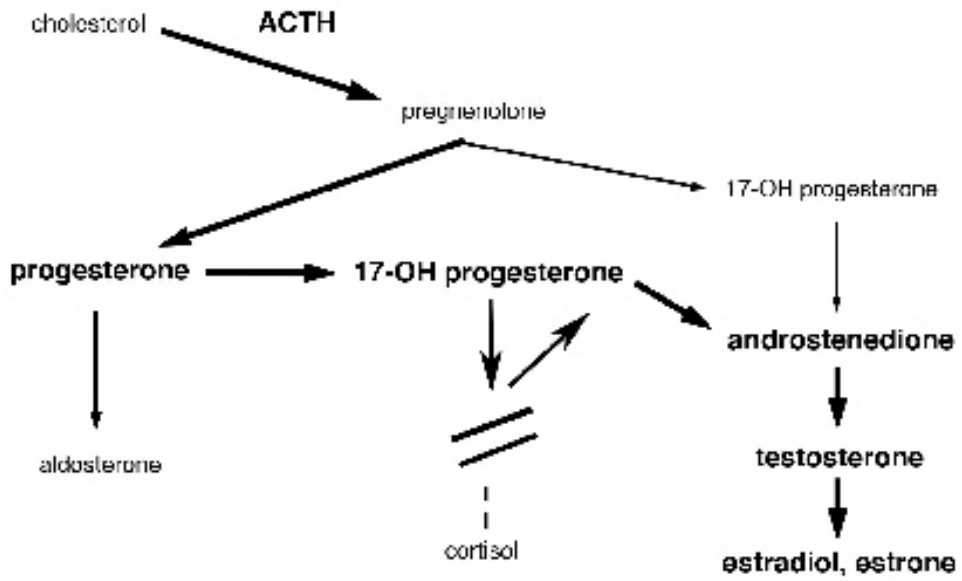
Dogs affected with SARD routinely present with signs suggestive of hypercortisolism (1,2,3,4,5) but only a minority are diagnosed with Cushing’s disease. (2,6) Early on, researchers speculated that this hypercortisolism was the physiological response to some unidentified stress (5). SARD-affected dogs also demonstrate elevated levels of adrenal sex hormones (androstendione, 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).

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) Based on clinical signs and diagnostic tests, this dog experienced the resistance phase during the first year of SARD. (table 4)

In the final phase—exhaustion—the adrenal glands are unable to sustain elevated cortisol production. For a short time, declining levels of serum cortisol fall within the normal range *giving the impression the dog has adapted*. Clinical presentation may temporarily improve. Once cortisol production falls *below* normal, clinical signs resurface as a result of accumulating sex-hormones — progesterone, androgens, and adrenal estrogen. (figure 1)

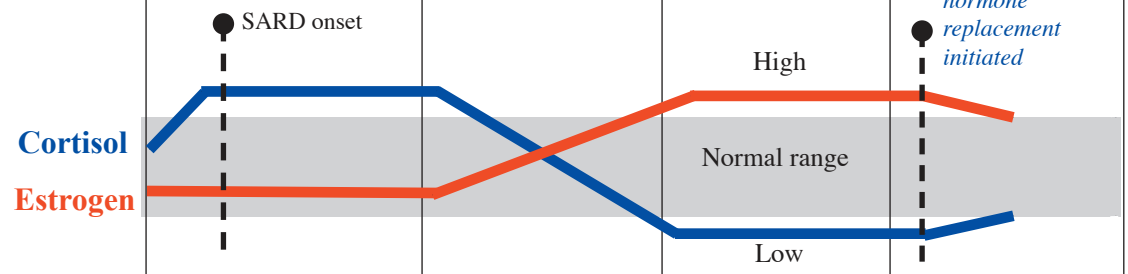
Figure 1. Sex-hormone accumulation during adreno-cortical exhaustion



The dog described here first entered the adrenal exhaustion stage during the second year of blindness. As cortisol production began to fail, clinical signs improved. By the third year, the dog developed advanced adrenal fatigue with elevated estrogen levels.

(Note: This time frame, in the author's experience, is *highly variable*. The dog described here developed adrenal exhaustion several years subsequent to SARD-onset. Other dogs reach this stage within weeks or months.)

Table 4. Adrenal activity during the three years post-SARD

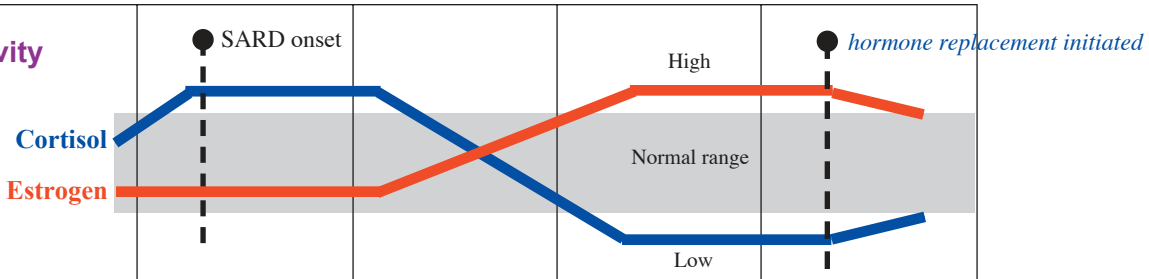
	First year post-SARD	**Second** year post-SARD	**Third** year post-SARD	**Fourth** year hormone replacement
				
	Resistance phase: Chronic stressors raise cortisol production, desensitizing the feedback loop. Elevated cortisol production continues unabated. Clinical signs mimic Cushing's disease, while diagnostic tests are negative or borderline.	**Exhaustion phase:** **— initial —** Cortisol production begins to fail, temporarily dropping within the normal range. Clinical signs resolve *giving the impression* the dog has adapted.	**— advanced —** Sex-hormone levels rise in response to continuous ACTH stimulation. Elevated estrogen increases clinical signs.	**Recovery phase:** The hypothalamus, perceives the presence of prescription glucocorticoids and reduces ACTH stimulation. Exhausted adrenal glands relax. Estrogen levels return to normal. Clinical signs improve.

Hyperestrogenism produces effects similar to hypercortisolism including, confusion, fatigue, depression, agitation, pancreatitis, and seizures in humans, (13-19) renal disease, and bone marrow depression in dogs (20,21); immunoglobulin suppression, hepatic dysfunction, increased mast cell activity, histimine release, and thyroid binding in both species. (12,16,22,23) Estrogen-treated rats experience PU/PD and an inability to concentrate urine. (24,25) Increases in related sex-hormones, such as progesterone, androstenedione, and testosterone cause increased heat intolerance, acne, obesity, and hirsuitism. (26, 27)

Severely depleted cortisol causes anorexia, abdominal pain, vomiting, diarrhea, organ failure, and weakness. Without treatment, severe hypocortisolism is fatal. (28,29) Hormone replacement therapy re-establishes glucocorticoid activity and normalizes excess adrenal sex-hormone production in both dogs and humans. (11,12,30,31)

Overview of case:

Clinical signs	Year 1	Year 2	Year 3	Year 4 *hormone replacement*
	polyphagia	resolved		
	obesity	resolved		
	heat intolerance	resolved		
	lethargy	resolved	lethargy	resolved 3 mo.
			pacing/agitation	resolved 3 mo.
			seizures	resolved 3 mo.
			anorexia	resolved 3 mo.
			hirsutism	resolved 3 mo.
			confusion	resolved 6 mo.
			head tics	improved 6 mo.
			GI upset	improved 6 mo.
Diagnostics				
ACTH-suppression	inconclusive		negative	
Low-dose dex.	negative			
Abdominal U/S			negative	
E&I panel			estrogen H cortisol L	Improvement in all parameters

Adrenal activity				
				
	Resistance: Chronic stressors raise cortisol production, desensitizing feedback loop. Elevated cortisol production continues unabated. Clinical signs mimic Cushing's, while diagnostic tests are neg. or borderline.	**Exhaustion: — initial —** Cortisol production begins to fail, temporarily dropping within the normal range. Clinical signs resolve during this time *giving the impression* the dog has adapted.	**Exhaustion: — advanced —** Sex-hormone levels rise in response to continuous ACTH stimulation. Elevated estrogen causes increased clinical signs.	**Recovery:** The hypothala-mus, perceives the presence of prescription glucocorticoids and reduces ACTH stimulation. Exhausted adrenal glands relax. Estrogen levels return to normal. Clinical signs improve.

CONCLUSION

This dog demonstrated an unmistakable pattern of stress adaptation during a three-year period following SARD onset. The period in which the dog was thought to have "adapted" to SARD was merely a transitory phase preceding complete adrenal exhaustion. Low-dose glucocorticoid and thyroid hormone replacement had a significant positive effect on both clinical presentation and laboratory findings. Owners should be encouraged to pursue adrenal estrogen testing and hormone replacement therapy for signs of excessive adrenal activity.

COMMENTS FROM THE DOG'S OWNER

Owner comments are not typically included in veterinary case reports, however, the following information may be beneficial to owners and practitioners considering hormone replacement for SARD-affected dogs.

October 29, 2007

Ms. Levin,

I just wanted to give you an update on Bud and to say thank you for all your help. You have given him back to me. In the last several weeks, he is acting so much like he did before he went blind.

I'm hoping your message is really heard by some of the vets. I wish we could have avoided this last year with all of Bud's upset stomach episodes.

Please, feel free to share my note. I hope that it spurs people to seek treatment. I couldn't imagine if I had found your information too late. I just wish I had found it sooner.

Best regards,
Kathy Moffet

ACKNOWLEDGEMENTS

The author wishes to thank E. Kuchenbrod DVM for her dedicated work in this case; E. Bentley DVM, A. vander Woert DVM, K. Abrams DVM, E. Holt DVM, A. J. Simpson DVM, and W. Dean MD for discussing their work in this area.

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SARD, adrenal activity, and hormone replacement – case report

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PURPOSE

Describe the pattern of adrenal activity, hormone replacement therapy, and outcome of one dog affected with Sudden Acquired Retinal Degeneration (SARD).

THE CASE

- 9 y/o neutered male Brittany Spaniel
- Fluctuating signs of adrenal activity during the three years post-SARD
- Negative for Cushing's disease
- Elevated estrogen and low cortisol via Endocrine & Immunology panel (National Veterinary Diagnostic Services, Quail Valley, CA)

Hormone replacement therapy was initiated by the general practice veterinarian to augment low cortisol and low-normal thyroid.

dexamethasone sodium phosphate 3.6mg IM
triamcinolone acetonide 0.3mg IM
methylprednisolone 2mg PO sid
levothyroxine 0.2mg PO bid

Endocrine & Immunology panel was repeated at three and six months.

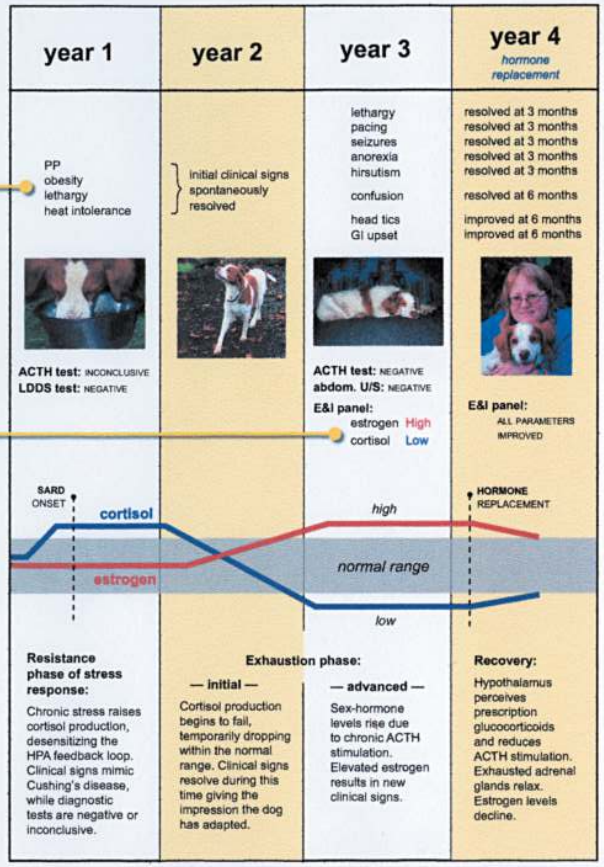
RESULTS

- Estrogen, cortisol, and immunoglobulins demonstrated a gradual shift toward normal.
- T3 and T4 rose to the mid-normal range.
- Owner reported complete resolution in 62% of adrenal signs and "some improvement" in 38% at three months. By six months, 75% of signs resolved.

	Initial	3-month	6-month	Normal range
cortisol	0.71	0.88	0.98	1.00–2.50 ug/dL
total estrogen	25.15	25.07	25.03	20.00–25.00 pg/mL
T3	110.09	115.73	121.16	100.00–200.00 ng/dL
T4	2.56	2.84	3.05	2.00–4.50 ug/dL
IgA	52	59	68	70–170 mg/dL
IgG	927	982	1,092	1,000–2,000 mg/d
IgM	93	97	101	100–2000 mg/dL

DISCUSSION

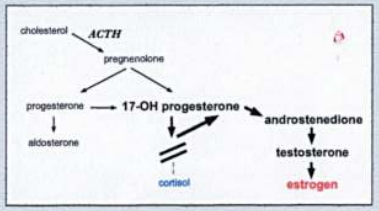
Signs of hypercortisolism are common in SARD cases. These dogs also demonstrate elevated adrenal sex hormones within the first year of blindness.[1] One explanation for this pattern is Selye's model of stress adaptation, which describes the progression from excess cortisol production to insufficient cortisol production—adrenal gland exhaustion.



The **resistance phase** follows a prolonged period of stress. The HPA feedback loop fails and cortisol production continues unabated.[2] The dog described here experienced the resistance phase during the first year of SARD.

In time, **adrenal exhaustion** develops. Cortisol production fails. Precursor hormones accumulate and are redirected to the sex-hormone pathway.

Adrenal sex-hormone production during exhaustion phase



- Elevated estrogen mimics the clinical signs of elevated cortisol including: PU/PD, PP, lethargy, depression, confusion, agitation, seizures, bone marrow and immunoglobulin suppression, histamine release, thyroid binding; renal, pancreatic, and hepatic disease.[3-14]
- Elevated progesterone and androgens result in: heat intolerance, acne, obesity, and hirsutism.[15-17]
- Severely depleted cortisol causes: anorexia, vomiting, diarrhea, weakness, organ failure, and death.[18]

The dog described here developed adrenal exhaustion in the second year of blindness. As cortisol production failed, clinical signs improved. By the third year the dog had developed advanced adrenal fatigue. This time frame is highly variable.

CONCLUSION

This dog demonstrated an unmistakable pattern of stress adaptation. Low-dose glucocorticoid and thyroid hormone replacement had a significant positive effect on both clinical presentation and laboratory findings. Owners should be encouraged to pursue adrenal testing and hormone replacement therapy for signs of elevated adrenal activity.

FUTURE RESEARCH

The author would like to collaborate on SARD cases at the time of onset. Interested parties please contact the author at: caroline@pelicanbooks.com

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The author wishes to thank E. Kuchenbrod DVM for her dedicated work on this case; E. Bentley DVM, A. vander Woert DVM, K. Abrams DVM, E. Holt DVM, A. J. Simpson DVM, and W. Dean MD for discussing their work in this area.