Acral Mutilation Syndrome

Introduction

Acral **M**utilation **S**yndrome is an inherited neurodegenerative sensory disorder that causes an insensitivity to pain and temperature. It is part of a group of sensory disorders that also occur in humans formally called **H**ereditary **S**ensory **A**utonomic **N**europathy, or simply HSAN. A protein called GDNF which lies within the brain becomes deficient and causes the sensory insensitivity. The type of HSAN found in five Sporting breeds was named AMS to describe the end results of this disease. English Cockers, English Springer Spaniels, English Pointers, German Shorthair Pointers, and French Spaniels have reported an incidence of this disease and were confirmed by DNA analysis. Recently, the Miniature Schnauzer was added to this group.

Symptoms

One reference stated symptoms can be seen as early as four months old when an affected pup will begin to lick and bite their paws. Another reference stated affected puppies appear smaller than healthy pups in the litter and the age of symptom onset varied from 2 to 12 months of age. It has also been stated that soon after birth affected pups will show a lack of response to a pinprick or compression. Affected pups can suddenly start intense licking, biting, and severe self-mutilation of the feet. There is a presumption that the feet/toes 'tingle' and it's that sensation that starts the process. Mutilation can lead to auto-amputation of the nails, digits, and footpads. Fractures can also occur in the toes and affected dogs will not feel a fracture. Secondary infections can result and be difficult to treat. Perhaps onset will be an individual response due to the gradual loss of the protein called GDNF. Once there is significant loss of protein self-mutilation results.

Treatment

There is no effective treatment. Management of the condition would involve some sedation, a cone, bandaged feet, or boots. Secondary tissue infections must also be managed. At some point in time the humane consideration is euthanasia. How does one manage an affected dog for its life?

Genetics

AMS is inherited as an **autosomal recessive disease**. Both parents must carry one copy of the mutation for the disease to occur. When each parent carries one copy of the mutation they are classified as CARRIERS and can potentially produce affected offspring depending on the genetic status of the partner. A carrier will not be affected with the disease, but they do pass their mutated copy to half their offspring. This is why it is VERY important to identify carriers before they are used. A carrier can be safely bred to a genetically Normal dog. No affected offspring will result, but more carriers will be produced. DNA testing should be utilized testing the offspring when any carrier is used. Testing puppies prior to placement will easily identify the status of each pup in a given litter. New owners can then be informed about the genetic status of their pup. If testing isn't done all pups placed should be spayed/neutered with a contract agreement. Our gene pool is small and removal of a carrier can result in further reduction of the gene pool and potentially cause a bottleneck. Remember, Carriers WILL

produce Normal offspring when bred to DNA tested Normal dogs. It's your job to identify the genetic status of each individual that results from this type of breeding. One can not predict statistically what the genetic outcome will be in any given litter without DNA testing. Statistical analysis is not absolute because it's essentially based on 100. Of great importance is the quality of the animal being considered for breeding. The Cocker should possess the essential elements that define what a cocker should be physically, mentally, and temperamentally. As the old saying goes: 'Don't throw the baby out with the bath water.' DNA testing can eliminate affected individuals dramatically. Maintain a healthy gene pool balancing desired qualities and traits through careful use of DNA tested individuals. It doesn't take long to see results. Below is an example of recessive breeding combinations.

	Clear Male	Carrier Male	Affected Male
Clear Female	100% Clear	50/50 Carrier/Clear	100% Carrier
Carrier Female	50/50 Carrier/ Clear	25/50/25 Clr./Carr./Affctd.	50/50 Carrier/Affected
Affected Female	100% Carrier	50/50 Carrier/Affected	100% Affected

Conclusion

There are no documented studies specifically naming English Cockers that have resulted in information to clearly define the disease. As mentioned, it may well mean it's an individual response with a general range of onset ages based on when GDNF deficiency begins and depletion is complete. Those with affected dogs need to share this type of information to better educate those involved with our breed and the veterinary community that desperately tries to treat affected dogs. At this point in time this condition has been identified in Field/Working Cocker lines. A long time Field enthusiast stated a case was seen 30 years ago in the UK, but no one knew what it was. Antagene (France) released the test as validated for Cockers in 2014. A French research group identified the mutation first in the French Spaniel. The study progressed to German Shorthair Pointers, English Springer Spaniels, and English Pointers. A 'founder effect' existed between these breeds. Other sporting breeds were then added to the study: ***A Point Mutation in a lincRNA Upstream of GDNF Is Associated to a Canine Insensitivity to Pain: A Spontaneous Model for Human Sensory Neuropathies.*** Of interest in this journal article the following was stated:

We started this project focusing our study on dogs with self-mutilations using a precise clinical questionnaire and we quickly detected that all dogs with self-mutilations also presented insensitivity to pain, not always reported. This important clinical sign led us to improve the genetic analysis. Indeed, we found additional affected dogs without self-mutilations but related to cases with self-mutilations. These dogs showed the "affected"

homozygous haplotype, while owners did not detect the insensitivity to pain. This observation reflects the difficulty to diagnose insensitivity to pain in dogs, which contributed to the spreading of this severe disorder in the four related breeds [18,19,21]. This feature led us to consider self-mutilation, probably triggered by small fractures of toes or other injuries [21], as a consequence of the insensitivity to pain. Translated, **Affected dogs don't always develop disease.** When a dog is DNA tested as AFFECTED, regardless of age, the dog should be removed from a breeding program. The test result is correct (unless contamination of the sample occurred) and the dog does indeed carry two copies of the mutation. There are theory's as to why such a dog doesn't develop clinical expression of disease, not necessarily pertaining to AMS. This also happens in other recessively inherited diseases. Mutations have a string of 'wanna be's' that follow them around waiting to contribute to the havoc. Sometimes these 'wanna be's' just don't get to make their contribution. Why? When that does happen the affected dog is lucky because it does not develop disease. It still has two copies of the mutation to produce disease. That is a really simplistic explanation, but it is easy to understand minus all the technical details. This scenario is typically rare, but it can happen in a DNA tested population for any disease condition. Most testing terminology today will classify an Affected animal as: Affected/At Risk. The 'At Risk' part is the rare 'maybe' that disease won't occur. Genetically affected and clinically affected are not the same. Most of these dogs are genetically affected and clinically affected. Unfortunately, there are reports of DNA tested Affected AMS Cockers that are older and they did not develop disease. We do not have these details. Costly research generally isn't done to find the reasons why 'affected' dogs don't develop disease. The mutation is there and informed breeding practices can eliminate both copies thereby eliminating the string of 'wanna be's.'

The Cocker Spaniel Club (British Parent Club) did inform owners about AMS in their 2015 Yearbook. To date very few 'show type' English Cockers have been tested. It's easy to assume a genetic defect isn't present when no one tests for it. Assumption is the mother of all evils. Perhaps it's time for show lines to also check breeding stock for AMS.

This is a horrible disease with horrible consequences. All Field Bred/Working Cockers should be DNA tested prior to breeding. Request/exchange test results before breeding. Don't buy a puppy unless the parents have been tested.

Laboratory Testing

OptiGen—DNA is sent to Antigene. www.optigen.com OptiGen pricing is Tier 2 and is based on the number of tests bundled. A 5% on line discount is given for one test, but two tests is a 20% discount. Email OG for details and if additional discounts are available. OptiGen is now a division of Wisdom Health.

Mars—The "panel" for English Cockers is $129.99. A discount code can be used: **optigen10** for a 10% discount. Note: if one wants to have prcd-PRA done as part of the panel of tests it would be an add-on for approx. $25. Mars is Wisdom Health.

Petagenics—AMS only: 38.08 US dollars www.petagenics.co.uk for information

Antagene—contact@ antagene.com Antagene may process all DNA tests for AMS.

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Embark—
https://embarkvet.com/contact/ Discount code pawsome20—$20 off on panel. You must search by using HSAN.
AnimaLabs-
http://www.animalabs.com/shop/dogs/acral-mutilation-syndrome-ams/

Additional Information
Most AMS testing is done on Field/Working Cockers in Great Britain.
Those tested through:
Antagene:
Tested: **995**
Clear: **827**
Carrier: 158
Affected: **15**

Animal DNA Diagnostics:
Tested: 126
Clear: 102
Carrier: 21
Affected: 3

Total Tested: 1121
Clear: 929
Carrier: 179
Affected: 18

Kennel Club (UK) Totals:
Tested: 587
Clear: 550
Carrier: 36
Affected 1

Kennel Club AMS and other DNA registry results:
https://www.thekennelclub.org.uk/health/for-breeders/dna-screening-schemes-and-results/dna-screening-for-breeds-s-z/spaniel-cocker-dna-screening/https://www.the-cockerspanielclub.co.uk/ams_update.htm

***https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1006482**

http://documents.irevues.inist.fr/bitstream/handle/2042/61953/AVF_169_3_04_cor-reard.pdf?sequence=3