Hepatocerebellar Degeneration
by Patricia Long, with contributions by many others
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One of the 6 week old pups isn’t acting quite right. He seems a little uncoordinated. The next day his head tilts a little and trembles occasionally. He is taken to the vet who finds nothing obvious to explain the pup’s symptoms and suspects an inner ear infection. Antibiotics are prescribed. The breeder questions if it might have been the vaccine he had last week or maybe the kind of de-wormer she used. Two days later the puppy is worse and another puppy shows similar symptoms. Fear that something contagious has taken hold of the litter is just the beginning of the nightmare for a breeder of a litter affected with hepatocerebellar degeneration (HCD).

Blood work may show an increased concentration of bile acids after fasting, and a high plasma concentration of ammonia. There is no treatment for HCD. The puppy’s condition continues to deteriorate: it cries; is unable to stand unassisted; has to be watched when it eats so it doesn’t aspirate food or water when its head bobs uncontrollably into the bowl; and finally peace comes to these affected puppies through euthanasia.

On necropsy, the disease has been found to have two main aspects. There is degeneration of the cerebellar cortex (cerebellar abiotrophy, or CA), and degeneration of the liver with secondary shunt formations. While CA has been found in many breeds, the hepatic degeneration in such young puppies is very unusual.

A common occurrence in affected HCD litters is stillborn pups. One breeder experienced an entire stillborn litter. The next repeat breeding had stillborn puppies, living affected puppies, and normal puppies. The pathology reports on some of the stillborns indicated that the brains were underdeveloped. It was assumed at the time that the stillborn was just a premature puppy. Is this part of the condition? Have other people had similar experiences? We don’t know. More input from affected litters is needed. There hasn’t yet been enough gathered information shared to identify all of the various aspects of this disease. Researchers are hopeful that articles like this one will prompt breeders to delve deeper into causes for stillborn pups and to report pups with HCD-like symptoms to researchers.

Dr. Paige Carmichael, a veterinary pathologist at the University of Georgia Veterinary School, Athens, GA, has been researching hepatocerebellar degeneration in Bernese Mountain Dogs for a number of years, and continues to study multiple aspects of it. The first reported case was from Switzerland in the 1970’s, and additional cases have been reported to Dr. Carmichael from Switzerland, Austria, Germany, as well as the United States. This disease is not isolated to one country, or to one line of Bernese.

To see specifics about HCD, read the detailed description of the disease in the 1999 October Alpenhorn, and the personal experience of one breeder in the 2001 October Alpenhorn. (These articles are available on the www.bmdca.org site under the health section. If you don’t have access to these sources, please contact Pat Long.) The 1999
article was published by Dr. Carmichael et al in the Journal of the American Veterinary Medical Association, Vol 208, No 8 (April 15, 1996). That article describes the findings from studies of three affected litters. She is continuing her studies of cases from around the world at the University of Georgia in an attempt to locate a genetic marker for this disease. Dr. Carmichael found that HCD is genetically based and probably autosomal recessive. This makes finding a marker to identify carriers much more likely than if the disease were polygenic like hip dysplasia. All affected litters that have been publicized since Dr. Carmichael’s initial research have also supported these preliminary conclusions. For the purposes of this article, I will use the assumption that this disease is in fact genetic and autosomal recessive.

HOW HCD is Passed to Puppies

Dogs have 39 pairs of chromosomes; one of each pair comes from the dam, the other from the sire. One pair of chromosomes is the sex pair, the XY pair. The dam (being XX) always provides the X, and the sire (being XY) provides either the X or the Y. All other 38 pairs are autosomal (non-sex-related chromosomes.) A recessive gene is one that has to be present on each of one chromosome pair. Therefore, the gene for an autosomal recessive trait must be provided by both the dam and the sire for a puppy to be affected.

Each parent of an affected litter must be a carrier of this trait. HCD as an autosomal recessive trait is unusual in that no affected pup has yet been able to live past the age of 3 months, so no affected dog has been bred. It is also important to note that symptoms of this disease are evident before any puppy is old enough to be placed. I have not heard of any affected Berner puppy that has been placed with a buyer prior to being identified as affected. Neither parent of any affected litters are affected. But they are BOTH carriers. There are four possible combinations for a pup to inherit the HCD genes(s) from two parents who are both carriers:

- a pup can get the HCD gene from the dam and a clear gene from the sire
- a pup can get the HCD gene from the sire and a clear gene from the dam
- a pup can get the HCD gene from both parents
- a pup can get the clear gene from both parents

So statistically, half of the pups in a litter produced by a carrier sire AND a carrier dam will have one copy of the gene and be carriers, 25% will be affected and die, and the other 25% will be clear of the gene. But statistics are the theory; in reality it's still possible to flip a coin 10 times in a row and get "heads" each time.

Assuming HCD is autosomal recessive, 1 in 4 pups from two carrier parents will die. Of those surviving puppies, 2 of the 3 are carriers. In other words, each surviving puppy in an affected litter has a 67% chance of being a carrier. Their offspring have a 33% chance, and each successive generation halves the carrier risk if no more carriers are added into the pedigree mix. Likewise, if a known carrier is bred to a clear dog, then each pup in the resulting litter will have a 50% chance of being a carrier, their offspring have a 25% chance, and each successive generation halves the carrier risk if no more carriers are
added to the pedigree mix.

What Can We Do Until We Have a Carrier DNA Test?

Without a genetic test, breeding an unknown dog to an affected dog is the most productive way to determine if the unknown dog is a carrier. We can't do that with this disease because the affected pups do not reach breeding age. But when we mate a dog whose status is unknown to a carrier (a dog who has produced HCD), we need to have 16 unaffected puppies to achieve a 99% confidence level that the unknown dog is clear. Test matings cannot prove the absence of a gene, they can only prove the presence of it when an affected puppy is produced.

Will a tight inbreeding help? If it results in affected pups, it will tell us both the sire and dam are carriers. If it doesn't produce affected pups, it tells us nothing. If the litter is 14 puppies and none is affected, it gives us a false sense of confidence that both the daughter and the sire are not carriers. In reality, the father could be a carrier and the daughter could be one of the 50% of his unaffected offspring clear of the trait, OR the daughter could be a carrier from her mother's line and the father could be clear.

Where did HCD originate? What lines are on top (sire's side) and bottom (dam's side) of the pedigrees of the affected litters? We are extremely lucky at this point. We have some breeders who care enough for the breed to openly share their information. There may be others out there with information, but they may not realize that this is a genetic disease, or that pups they have had with the symptoms of HCD had a diagnosable disease at all. Each known carrier helps us learn better how to avoid producing more affected puppies. Without a genetic test, knowing how to avoid doubling of carrier lines in both the sire's and dam's sides of a planned pedigree is especially important. We owe a tremendous debt to each person sharing this information.

1988 litter:

- Majanco Languardo
- Pike's Barnard O'Languardo
- Pike’s Elsa V Siegfried (to Edo x Christine)
- Bev’s Baron V Greybern
- Grey V Waldacker
- Greta V Rosiendlithal
- Berna V Rosiendlithal

Affected litter

- Majanco Languardo
- Pike’s Bordeaux O’Languardo
- Pike’s Elsa V Siegfried (to Edo x Christine)
- Bev’s Latest Edition V. Jodi
- Darius Of Rutherford (to Edo & to Christine)
- Bev’s Jabbering Jodi V Bb
- Alphorn’s Happy Talk

1989 litter:

- Faro v Hurstfeld of Sinova
- Majanco Languardo
Erika v Schnetzenschachen
Pike's T-Total Traum O'T-Bis
Pike's Siegfried v Edo (out of Edo x Christine)
Pike's Elsa v Siegfried
Bella's Albertine Faymie

Affected Litter
Basco v Bifang
Rex v Barenried
Fanta v Hogerbuur
Pike's Pioneer Spirit v Rex
Pike's Siegfried v Edo (out of Edo x Christine)
Pike's Melissa v Siegfried
Pike's Amanda O'Languardo (out of Majanco Languardo)

1994 litter:
Pike’s Chewbacca (out of Majanco x Christine)
Arak's Bittersweet Beau
Thistledown El Maximillion
Dominic V Adonis (to Edo, Christine)
Thistledown’s Celeste V Pike
Pike’s Angelica O’languardo (to Majanco, Edo, Christine)

Affected Litter
Barnard O’languardo (to Majanco, Edo, Christine)
Bev’s Baron V Greyburn
Greta V Rosiendlithal
Thistledown Klever Karli
Jaycy’s Wyatt Vom Hund See (to Edo, Christine)
Arak Lagniappe V Thistledown
Durrbach’s Christine V Beau (to Majanco, Christine)

1999 litter:
Dallybeck's Echo Jackson (to Edo & Christine)
Abbey Rd Here Comes the Sun
Garissa Just a Little Crush
Sandusky’s Diamond Rio
Bev’s Royal Sun Fendi v BB (to Majanco, Edo, Christine)
Sasha’s George v Bev
Sasha’s Belleminerva
Bugziere Erika v Bev
Bev’s Thor Artanz of Maine (to Majanco, Edo, Christine)
Mentmore’s Apple Blossom v Bev’s
Mentmore’s Lovage (to Majanco, Edo, Christine)

Affected litter

1999 litter:
Rosco Vd Schwarzwasserfluh
October Blue Mt’s Made To Win
Nor-ham October Cover Girl
Sunshine's Mt Shasta Born To Win
  Bev's Baron V Greybern (to Majanco, Edo, Christine)
Sunshine's Luvly Rita V Bev's
  Bev's Dixie Melody V Hope (to Majanco, Edo, Christine)

Affected litter
  Dallybeck's Echo Jackson (to Edo, Christine)
  Swiss Star's Nitro Whatagas
  Vombreiterweg's Swiss Lace
  Blackcoral A Lady Go Diver, Cd
  Deerpark Blackcoral Dive Kru (to Edo and littermate Diana, Christine)

Oro Valley Blackcoral Remora
  Rosewood Dorrah (to Diana, Edo)

2002 litter:
  Jamars New Flash V Wyemede (to Edo & Christine)
  Deep Valley Jason
    Jamars Lady Luck (to Majanco, Edo, Christine)
  Jamars Tobler
    Hope's Chessmaster (to Majanco, Edo, Christine)
    Jamars Gidget V Hope
    Hope's Smurffet (to Majanco, Edo, Christine)

Affected litter
  Abbey Rd Here Comes The Sun (to Edo & Christine)
  Bev’s Royal Sun Fendi v BB
  Bev’s Royality v Bb (to Majanco, Edo, Christine)
  Jamars Royal Fen-Del V Bev’s
    Bev’s Baron V Greybern (to Majanco, Edo, Christine)
    Bev’s Royality v Bb
    Arak’s Helga V Bev’s (to Majanco, Christine)

2002 litter:
  Pfalz-tiegaan Vom Heideborn
  Paradis Axi V Nordstaaten
    Brione Lisaal Von Den Ahlwiesen
  Avalon’s Mi-heartbreaker
    Brandywine Chauncy Brown (to Majanco, Edo, Christine)
  Avalon’s Under Mi-spell
    Avalon’s Mi-bewitched

Affected litter
  Bev’s Royal Sun Fendi v BB (to Majanco, Edo, Christine)
  Jamars Royal Fen-Del V Bev’s
    Bev’s Royality v Bb (to Majanco, Edo, Christine)
  Avalon’s Mi-lady V Jamar
    Mountain Lore’s Gentle Joshua (to Diana)
  Avalon’s Mi-dream Come True
    Avalon’s I Dream of Jeanie

What can we learn from these? Many of our lines go back to all of these dogs. Not every Berner that goes back to these dogs is a carrier. Are these lines the source of the HCD gene in Bernese? Perhaps, perhaps not. Are these lines still present in European dogs? Although she does not share pedigrees and maintains confidentiality in her research, Dr. Carmichael has stated that she has had affected litters reported worldwide. Do we have
affected litters that do not go back to these dogs? We may never know, or we may someday get information about an affected litter that helps answer some of these questions. For now, breeders with these dogs in their pedigrees have several choices which include ignoring this disease because it is a breeder's problem and never affects puppy buyers, unless, of course, the puppy buyer is a breeder. Other choices include trying to avoid placing known carrier lines (the Edo v Moosseedorf and Diana v Moosseedorf breedings.) in the top AND the bottom of a pedigree. Perhaps a more practical approach is to start talking about this disease with other breeders with whom they work and assessing familial risk based on incidence of affected or stillborn puppies in carrier lines. Not all dogs from carrier lines are carriers. The more open we are with one another about this and other diseases in our breed, more informed choices and potentially reduced risk can be achieved. Sharing information about affected litters and assisting in research efforts are ways that we can hope to ever help breeders avoid producing the disease.

What else can you do? When you acquire a puppy that you eventually hope to breed, ask the breeder to give you the names and contact information of the owners of the littermates so that you can keep in touch. Sometimes the breeder leaves the breed or may not be interested in sharing news with other littermate owners. Make sure you can find out about the health and production records of your dog's littermates.

Dr. Carmichael continues to study this disease in our breed. She is available for consultation and would appreciate being contacted immediately when affected puppies are suspected by any breeder. Her research is confidential, and although she will need the pedigree information of an affected puppy, she does not share any information with anyone else. The pedigrees shared here came to the author directly from the breeders of these litters. Dr. Carmichael is NEVER the source of pedigree information. But you can share it openly, and help others to avoid the same problems. Don't expect anyone else to share if you're not willing to share as well!

As one of the breeders of an affected litter told me: “Addressing HCD will not be nearly as hard as many other things we would like to address....like malignant histiocytosis. For me since the very beginning of my awareness of the hereditary nature of cerebellar disease, I've felt it could be successfully addressed BECAUSE the affecteds don't live. What a
blessing their passing from this life is. Minimizing their suffering and the suffering of my fellow breeders by facilitating widespread understanding of how this disease presents itself in young Berner pups has been my goal. We owe affected pups swift euthanasia. We owe our fellow breeders and future breeders our support in finding a carrier marker for this disease. It's not only possible. It's probable with a little help."

THE RESEARCH.
Currently, Dr. Carmichael is working on developing a carrier test, for which she needs fresh blood samples. Blood from a dam or sire of an affected litter can assist in this research, but the blood has to be very fresh for this test and has to be shipped overnight on ice to Dr. Carmichael at the University of Georgia in Athens. Submission of affected puppies for post mortem study will also aid in a better understanding of this disease. Whole body submissions are best, or if the veterinarian performs the necropsy then submission of all tissues including brain, liver and adrenal glands will also be beneficial. All tissues should be shipped in formalin, on ice - not frozen. At this time Dr. Carmichael is most interested in affected puppies and the stillborns from suspected pedigrees.

One of the most difficult aspects of some types of research is the “therapeutic trial.” Dr. Carmichael has a protocol developed, but it needs to be tested. For those trials very young affected puppies will be needed to undergo treatment protocols Carmichael is developing. Additionally, Dr. Carmichael would like to be able to breed affected litters, herself, in order to start therapeutic trials on affected puppies as early in the disease process as possible.

If you need additional information about the disease or the protocols, please contact Pat Long in order to minimize demands on Dr. Carmichael's time. If time is critical or you have affected puppies for which you need to work directly with Dr. Carmichael, please contact her directly at 706-542-5834 (office) or 706 542-6373 (lab), or email her at kpc@vet.uga.edu. For additional information about what is needed to help Dr. Carmichael's work, see the BMDCA website.