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Purpose of the research

Malignant histiocytosis is a severe progressive and fatal disease which isinherited by polygenetic inheritance in the Bernese Mountain dog.

Most dogs with this disease are presented to their veterinarian with markedweight loss, loss of appetite and pale mucous membranes. Tumors can arisefrom most types of tissue in the body but often tumors are found in the chestand in the abdomen, predominately in the spleen, liver and lymph nodes. Atthis stage the dog is often very weak and therapy is seldom instigated. Currently the only choice of therapy is chemotherapy. Unfortunately chemotherapy has not been very efficacious against this tumor form andmany dogs are left untreated and euthanized within a short time frame.

To summarize; Malignant histiocytosis is often silently progressive until thestage where the dog is terminally ill and where therapy has no hope inreversing the progressive nature of the disease.

We are therefore keen to find a way to diagnose the disease at a much earlierstage, this would represent a paradigm shift in how the disease is approachedin the Bernese Mountain dog. If the disease could be caught early it wouldallow therapy at an earlier stage. Instigating therapy while the tumor burdenin the body is low could result in a much longer disease free survival or at besta cure. Thus, having information regarding subclinical (undetected) disease ofa Bernese Mountain dog with malignant histiocytosis has the potential tomarkedly impact survival and prognosis.
In human cancer research several diseases such as prostate cancer and breastcancer have shown to have circulating proteins or sugars in the bloodcirculation which can predict that the person is suffering from cancer prior toactually detecting the disease. In fact, this has also been detected in human malignant histiocytosis where researchers in some types have found elevationof certain proteins prior to disease recognition.

Working hypothesis

The working hypothesis of this study is, that there exist blood borne biomarkers (molecules of either protein or carbohydrate origin), which can predict that Bernese Mountain dogs are going to develop malignant histiocytosis.

The study therefore aim to find a way to determine if a dog is ill before it in fact shows any signs of developing illness. If we can detect disease at such an early stage it may be possible to instigate therapy much sooner and this may as well have a major impact on the survival of the dog.

Scientific program

The content of this scientific program should not be published without prior consent from the research group

Research group
PhD student Lise Nielsen DVM, CertSAM
Main supervisor Professor Annemarie T Kristensen DVM PhD DACVIM -SA, DipECVIM-CA
Supervisor Professor Asger Lundorff Jensen DVM, Dr. Vet. Sci. PhD, DipEC VIMCA
Supervisor Senior Lecturer Fintan McEvoy MVB, PhD, DVR, DipECVDI
Supervisor Professor Merete Fredholm DVM, Dr. Med. Vet., PhD

Study period
Study start: October 2006
Study finished: approximately October 2009

Ethical consideration
This study has been approved by the Ethical and Administrative committee Dept. of Small Animal Clinical Sciences, University of Copenhagen and by the Danish council of animal trials.

Study population I
The study consists of two parts:
Part A:
10 Healthy old Bernese Mountain dogs over 10 years of age without disease are examined and blood sampled. The blood results from these dogs are compared to the blood results from sick dogs with malignant histiocytosis. Bernese Mountain dogs over 10 years are selected as these dogs are less likely to suffer from malignant histiocytosis. Aberrations in the normal blood profiles between these populations may give indications to which parameters are altered in sick dogs. These parameters are monitored closely in the healthy dog population (part B).
The older dogs and sick dogs are recruited over 3 years and will enter the study when possible.

Part B:
Thirty 4-6 year old healthy dogs are followed prospectively for two years. These dogs

are examined every 6. months. These dogs consist of two populations: one population from ancestors with a low prevalence of malignant histiocytosis and another population from dogs with ancestors WITH malignant histiocytosis (information obtained from a questionnaire study performed prior to initiating the PhD project).

The dogs are recruited at the start of the study and will be followed for 3 years.

Study procedures
Both part A and part B:
Screening to detect if the dogs have malignant histiocytosis involve clinical examination and diagnostic imaging (radiographs of the chest and ultrasound examination of the abdomen).
If the diagnostic tools identify masses, these lesions are examined by biopsy and subsequently submitted for tissue analysis.

Screening to screen for biomarkers involve an extensive blood panel (haematology, biochemistry and haemostatic parameters).

All animals in the study have frozen blood stored available for genetic analysis at a later date. The genetic profile of each dog, whether they develop malignant histiocytosis or not, may have an impact on the ability to produce blood borne biomarkers or biomarkers indicating that they are protected from developing disease and can aid in the prevention of the disease in the future.

Detection of disease
If malignant histiocytosis is diagnosed in the study population, appropriate therapy (chemotherapy) is offered to the dogs. This however is not part of the study.

Time line

October 2006 - August 2007
Recruitment of healthy dogs by letter
Article in the Danish Bernese Mountain magazin e
Article in the Danish Veterinary Magazine
Day seminar in the Danish Bernese Mountain dog club
Recruitment of Master students to participate in the 1st screening visitation

September 2007 - January 2008
Screening of healthy dogs 1st visit

February 2008
Data processing
Abstract accepted at American College of Veterinary Internal Medicine regarding protein loss in the urine in Bernese Mountain dogs. Presented June 2008 San Antonio, USA.
Recruitment of Master students to the 2nd screening visitation

March 2008 - June 2008
Screening of healthy dogs 2nd visit

July 2008 - August 2008
Data processing
Recruitment of Master students to the 3rd screening visitation.

September 2008 - December 2008
Screening of healthy dogs 3rd visit

January 2009 - April 2009
Data processing
Externship in tissue analysis to improve the understanding of malignant histiocytosis
Publication of work
Thesis manufacturing

Through-out the whole period
Screening of sick dogs with malignant histiocytosis Screening
of healthy dogs over 10 years of age