

AKC Canine Health Foundation Progress Report

<u>CHF Grant Number</u>	CHF Grant No. 02232-MOU
<u>Project Title</u>	Clinical and Pathological Characterization of Upper Airway Syndrome in Norwich Terriers
<u>Institution</u>	Michigan State University (University of California Davis, Texas A&M, University of Pennsylvania)
<u>Investigator(s)</u>	B J Stanley (MSU), NC Nelson (MSU), LR Johnson (UCD), KM Thieman (TAMU), D Holt (UPenn), M Mison (UPenn), D Agnew (MSU)
<u>Project Start Date</u>	February 2016
<u>Report Number</u>	Midyear 2
<u>Current Date</u>	May 2nd, 2017

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Study Objectives

Objective 1: Document and describe the clinical presentation and detailed upper airway endoscopy in Norwich terriers. This will be achieved by conducting standardized history questionnaires, physical examinations and upper airway endoscopy in North American Norwich Terriers (n=150), in stratified age groups. These data will then be used to develop a scoring system for severity of NTUAS.

Percent completion: we have recruited 132% (232 of the desired 175 dogs) into the study through REDCap (online clinical trial database). However, some of these recruited cases withdrew from the study due to different factors. We also lost contact with some of these. Of 232 dogs, 115 have already been enrolled and undergone their examinations and 16 are booked for enrollment which will be examined in late May through August 2017. Thus Objective 1 is 66% completed.

Objective 2: Results of rhinomanometry, head and neck CT, and upper airway endoscopy will be compared between Norwich terriers, Norfolk terriers, brachycephalic dogs and healthy mesaticephalic dogs. NTUAS dogs (n=25), age-matched Norfolk terriers (n=25), age-matched brachycephalics (n=25) and age-matched healthy mesaticephalics (n=25) will undergo rhinomanometry, head and neck CT and upper airway endoscopy. Data from each diagnostic test will be compared between the groups, to determine degree of intranasal obstruction or brachycephaly.

Percent completion: we have performed rhinomanometry and CT on 3 brachycephalics, 1 mesaticephalic, 2 Norfolk terriers and 4 Norwich terriers. However, there are so many variables encountered in performing rhinomanometry. After the eliminations of tubing/adaptor/connector errors, the unstable performance of the pneumotachometer lead us to inconsistent baseline data. The rhinomanometry data collected from those 10 dogs were considered invalid. Case accrual for Objective 2 has been delayed by several issues, including difficulties with the pneumotachometer and a failure of the MSU CT Scanner in 2016 Fall. However, a new CT scanner has been installed at MSU and now working well. We have performed head CT on 12 Norwiches, 4 Norfolks, 2 mesaticephalics and 9 brachycephalics; thus Objective 2 is 27% completed.

Objective 3: Describe the pathology seen in tissue collected from affected dogs and compare to tissues from control groups. The histopathology of any NT laryngeal tissues (sacculles, soft palate, supra-arytenoid tissues, and any whole larynges made available from post mortem tissues) will be descriptively compared to normal laryngeal tissues on file.

Percent completion: We have submitted sacculles from 44 affected Norwich terriers and 7 brachycephalic breeds. We cannot estimate percent completion as we do not know how many of the remaining dogs will require saccullectomy. Preliminary histological findings (NT=22, BAS=4) to date do not appear to be different between Norwich terriers and brachycephalic breeds.

Objective 4: Collect pedigree information and blood for DNA extraction. Previous studies suggest that dog morphology is highly heritable. Using genetic markers associated with body size and skull morphology, we will profile participants' morphology from a genetic perspective. Due to high breed specificity of the condition, it is likely that genetic investigations and pedigree analysis will prove a

mode of inheritance - and could identify causal gene mutation(s) and/or genetic modifiers of disease risk. DNA will be banked from all study participants for future investigations.

Percent completion: Blood has been drawn and DNA extracted and banked from all enrolled cases. Objective 4 is 66% completed. Pedigrees are still being collected from all enrolled cases and will be collated toward the end of the study.

Study objective 2 have mildly changed since the submitted application due to technical difficulty and inconsistency of pneumotachnometer. After discussion with NC Nelson (Co-PI) we decided to forgo the rhinomanometry.

Scientific Report (Confidential):

The recruitment of this study has been gradually plateaued since majority of age groups were fulfilled for enrollment: <1 yr (30/30), 1-2 yr (30/30), 3-4 yr (30/30), 5-7 yr (24/30), >8yr (27/30). The progress has followed the NTUAS Study time schedule appropriately. UCD and Texas A&M have both already completed their required numbers of enrolled dogs but are willing to examine more. UPenn started their first Study day on October 31st, has scoped 17 dogs. However, there are 14 dogs previously recruited to UPenn decided to withdraw from the Study. We will start contacting previously recruited Study subjects to fill those positions in each age strata.

As the primary institution, MSU has moved on to performing CT of head on several Norwich Terriers which were selected randomly in Study group and Norfolk Terriers in Control group.

We have not formally analyzed the results of the laryngoscopic examinations at this stage, but we can anecdotally report that the vast majority of larynges in the Norwich terrier breed are abnormal. The final results of the histopathology of excised sacculi are still pending; but with the comparison to other breeds, the preliminary results showed that there was no difference in histology between Norwich Terriers and brachycephalics. It is too early to report any results from CT data, although early subjective comparison of the CTs show anatomical laryngeal differences in the NT compared to other breeds, and no evidence of stenotic nares, or excessive and aberrant nasal turbinates, which are seen in the brachycephalic breeds.

Plan is to continue to accrue cases through until 2017 summer. The data will be analyzed at that time.

Non-Confidential, Lay language Progress Summary

The enrollment has followed the NTUAS Study time schedule appropriately. UCD and Texas A&M have both already completed their numbers of enrolled but both Drs. Johnson (UCD) and Thieman (TAMU) are more than happy to examine more dogs if they are enrolled. UPenn started their first Study day on October 31st, followed by 17 recruited cases which were all seen and examined to date. There are 14 dogs previously recruited to UPenn withdrew from the Study. Which creates more available positions in each age strata. MSU, the primary institution, is still accruing cases. With respect to age strata, we

have fulfilled majority of the age group: were fulfilled for enrollment: <1 yr (30/30), 1-2 yr (30/30), 3-4 yr (30/30), 5-7 yr (24/30), >8yr (27/30). After the age group being filled, we will accept dogs into the data but the NTUAS Study will not be able to fund these dogs.

As the primary institution, MSU has moved on to performing CT of head on several Norwich Terriers which were selected randomly in Study group, Norfolk Terriers and brachycephalics in Control group. Due to technical difficulties and inconsistent performance of the pneumotachometer (airflow pressure measuring machine), we decide to forgo rhinomanometry and keep CT only in our Study Objective 2.

We have not formally analyzed the results of the laryngoscopic examinations at this stage, but we can say that the larynx is widely affected within the breed. We also believe that the Norwich Terriers who showed their signs at younger age (<1 year of age) have higher incidence of presenting more severe clinical signs or laryngoscopic findings. There were total 31 resected tissues sent to pathology (44 from NT, 7 from brachycephalic dog) and the final report is pending. But the preliminary results showed that there was no difference in histology between Norwich Terriers and brachycephalics.

It is also too early to report any results from the CT data, although early subjective comparison of the CTs show anatomical laryngeal differences in the NT compared to other breeds, and no evidence of excessive nasal turbinates or stenotic nares which are seen in the brachycephalic breeds.

Publications:

No manuscripts are being prepared at this stage.

Presentations:

Future presentation:

1. Clinical and Laryngoscopic Characterization of Norwich Terrier Upper Airway Syndrome (NTUAS): (updated preliminary results). Society of Veterinary Soft Tissue Surgery (SVSTS). Jun. 2017.

The following presentations have been given:

1. Clinical and Laryngoscopic Characterization of Norwich Terrier Upper Airway Syndrome (NTUAS): Preliminary Results in 61 dogs. Poster Presentation. Veterinary Comparative Respiratory Symposium (VCRS). Sept. 2016.
2. Upper airway studies at MSU – what you can do to help. Presented to the MSU hospital staff and faculty at the beginning of the study. Nov. 2015

No Cost Extension Request:

Requests for CHF Assistance:

Not requested