MYOPATHY OF THE SCHAPENDOES BREED DOG, a differential diagnosis for hepatic disease as the cause of serum ALAT increase

Pernilla Syrjä *Veterinary Pathology Dept. of Veterinary Biosciences, University of Helsinki, Finland*

Tarja Jokinen *Dept. of Equine and Small Animal Medicine, University of Helsinki, Finland*

Maria Kaukonen *and* **Hannes Lohi** *Department of Clinical and Medical Genetics, Faculty of Medicine, University of Helsinki, Folkhälsan Research Center, Helsinki. Finland.*

Introduction: Breeders of the Schapendoes breed dog in Finland reported variable exercise- and heat intolerance in conjunction with elevated alaninaminotransferase (ALAT) in young dogs. Liver biopsy did not reveal consistent lesions explaining the elevated enzyme level. As some dogs' clinical signs progressed and the owners elected euthanasia of their pet, we investigated the clinical, histopathological and genetic findings of the cases further.

Material and Methods:

- **Liver biopsy and serum biochemistry** of seven Schapendoes dogs: age average: 3.7 years, range: 0.5-7 y., 2 females, 5 males.
- **Muscle biopsy and autopsy** of four affected Schapendoes: age average: 4.5 years, range: 3-5 y., 1 female, 3 males.
- **Genetic tests** based on DNA samples from 20 cases and 16 controls. Genome-wide association study (GWAS) and whole genome sequencing (WGS).

Results:

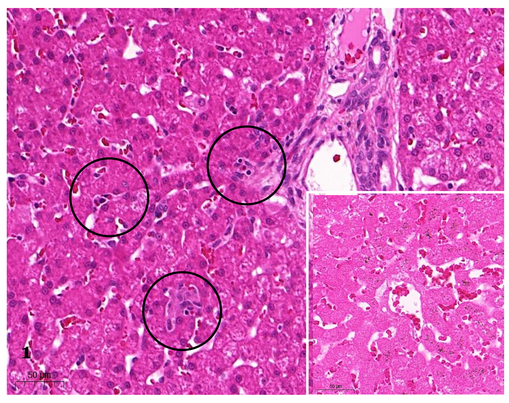

Fig.1: Very mild multifocal lymphohistiocytic chronic hepatitis (black circles) with mild centro-lobular copper increase (Inset: black granularity in hepatocytes) was diagnosed in two cases. Liver, affected Schapendoes, HE. Bar 50 µm. Inset: Liver, affected Schapendoes, Rubeinic acid stain.

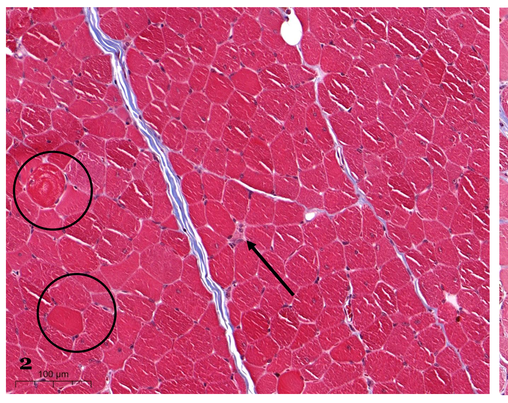

Fig.2: Mildly affected skeletal muscle showing scattered internalized nuclei, occasional hyalinized, round fibers (black circle) and occasional severely atrophic fibers (arrow). *Vastus lateralis,* affected Schapendoes, Masson stain. Bar 100 µm.

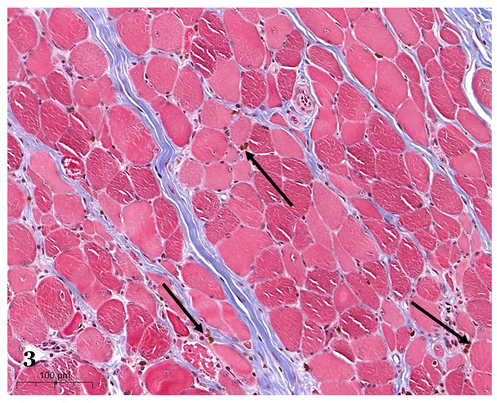

Fig.3: Severely affected skeletal muscle showing numerous internalized myocyte nuclei, marked variation in myofiber size, peri- and endomysial fibrosis and multifocal perivascular hemosiderosis (arrows). *M. deltoideus,* affected Schapendoes, Masson stain. Bar 100 µm.

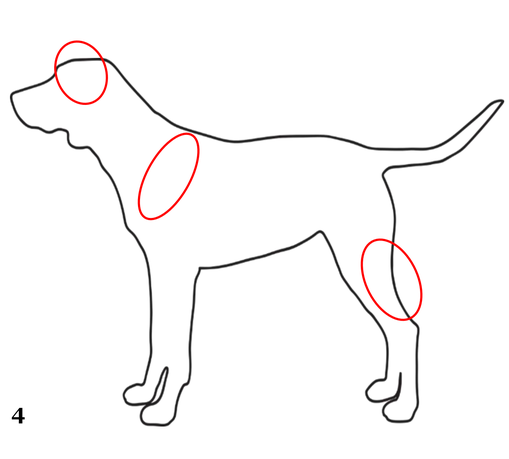

Fig.4: The pattern of most severely affected muscles in the examined Schapendoes dogs. Most severely affected were (indicated in red) deep digital flexors of the hindlegs, the muscles of the shoulder, and masticatory muscles. Schematic drawing of a dog.

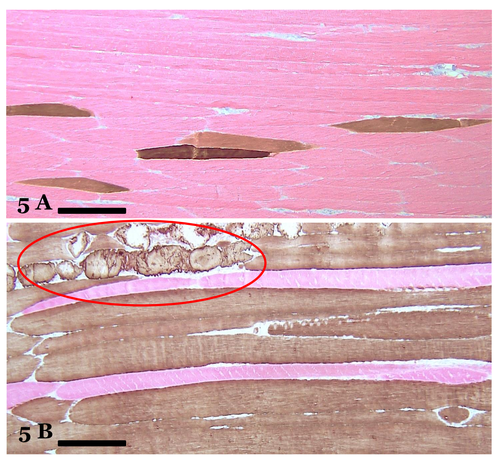

Fig.5: Fiber typing of skeletal muscle revealed that muscles with predominantly type I slow fibers were more severely damaged **(5B**) than muscles with predominantly fast contracting type II fibers (**5A**). IHC affected dog, skeletal muscle:anti-MYH7slow, revealed with DAB (brown), anti-MYH-2x fast, revealed with Fast red (red). Bar 100 µm.

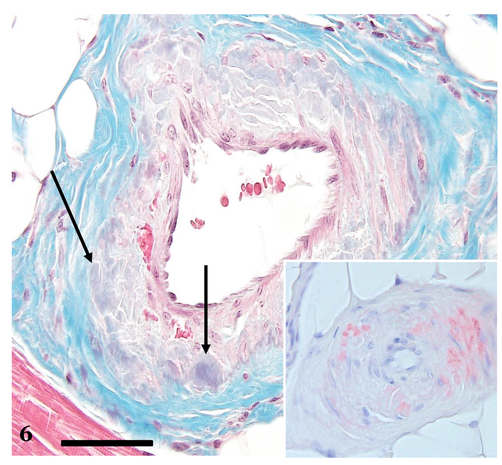

Fig.6: Vascular lesions consisted of periarteriolar fibrosis, degeneration of tunica media (arrows) and intramural hemorrhage in scattered arterioles of liver and muscle. Artery of skeletal muscle, Masson stain. Bar 50 µm. Inset: Kongo-positivity in the degenerated tunica media, indicating mild vascular amyloidosis. Kongo stain.

Further results:

- **Serum biochemistry:** moderately increased creatin kinase (CK): average 3807 U/l, range:1543-4876 U/l (ref. 60-235 U/l).
  Markedly increased ALAT: average 892 U/l, range: 150-1678 (ref. 18-77 U/l)
  Markedly increased aspartate-aminotransferase (ASAT): average 291 U/l, range: 63-706 (ref. 17-54 U/l)
- **Pedigree analysis:** suggested autosomal recessive inheritance.
- **GWAS:** all genotyped cases shared a 0.76Mb homozygous haplotype block absent in controls.
- **Filtered WGS:** a candidate causal variant was identified in a known myopathy gene of man.

Conclusions:

- A progressive degenerative myopathy occurs in the Schapendoes breed dog.
- Affected dogs present with elevated ALAT, ASAT and CK, in conjunction with variable exercise- and heat intolerance.
- Postural muscles and masticatory muscles are most severely affected, showing endo- and perimysial fibrosis, myocyte atrophy and degeneration.
- Arteriolar degeneration and fibrosis can be found in liver and skeletal muscle in advanced cases.
- The liver is not consistently affected, despite serum ALAT and ASAT elevation.
- Pedigree analysis suggests an autosomal recessive inheritance of the disease and a candidate causal variant is being validated.

HELSINGIN YLIOPISTO
HELSINGFORS UNIVERSITET
UNIVERSITY OF HELSINKI
ELÄINLÄÄKETIETEELLINEN TIEDEKUNTA
VETERINÄRMEDICINSKA FAKULTETEN
FACULTY OF VETERINARY MEDICINE